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Polymères pH-sensibles : Caractérisation et précipitation en milieu aqueux

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Résumé

Dans l'industrie pharmaceutique, de nombreux polymères sont employés pour l'encapsulation de molécules actives. Le choix des polymères est fonction de leurs caractéristiques et des applications visées pour les produits élaborés. Parmi les polymères utilisés, on retrouve les copolymères d'acide méthacrylique et leurs esters connus sous le nom d'Eudragit®. Les Eudragit sensibles au pH sont utilisés dans diverses formulations à des fins d'enrobage, de revêtement entérique, de masquage de goût, ou comme vecteurs thérapeutiques de principes actifs pharmaceutiques pour l'amélioration de la perméation à la peau, aux villosités intestinales ou encore à la cornée. Les Eudragit E100 et L100 notamment ont été étudiés de manière approfondie pour leur caractère hydrophile/hydrophobe en fonction du pH et de la salinité pour l'enrobage. Toutefois, la possibilité de préparer des particules sensibles au pH à partir de ces polymères n'a pas été systématiquement explorée en raison de la difficulté résidant dans leur précipitation sous forme de (nano)particules. Ainsi, ce travail de recherche a pour objectif de conduire une caractérisation physico-chimique complète et d'étudier différentes voies de préparation de (nano)particules d'Eudragit E100 et L100 en solution aqueuse par précipitation. Dans la première partie de notre étude, nous nous sommes attelés à clarifier les domaines de solubilité et de précipitation des deux copolymères. Nous avons pu observer que la concentration en polymère, le pH final du milieu ainsi que le temps d'incubation influencent la solubilité des Eudragit E100 et L100. La titration des 2 copolymères nous a permis de doser les fonctions carboxylates de l'Eudragit L100 et amines de l'Eudragit E100. De plus, l'impact de divers paramètres tels que le pH, la concentration en polymère et la force ionique du milieu sur la précipitation a été étudiée. Dans une seconde partie, l'influence de divers polymères secondaires sur la complexation et les propriétés colloïdales des particules d'Eudragit E100 et L100 a été étudiée. Dans ce cadre, le polyéthylèneimine a montré sa capacité à complexer l'Eudragit L100 donnant des dispersions stables et des tailles de particules submicrométriques. Dans un troisième temps, l'effet des tensioactifs sur la précipitation des deux polymères a été étudié. Ceci nous a permis d'identifier la nature des interactions impliquées et le mécanisme de complexation des deux Eudragit E100 et L100 en fonction de la concentration en tensioactif.

Mots clés : Eudragit, Précipitation, Polymères pH-sensibles, Polyplexes, Complexes Polyelectrolyte -Tensioactifs.

Abstract

In pharmaceutical industry, many polymers are used for the encapsulation of active ingredients. Polymers' choice depends on their characteristics and the intended applications of the developed products. Among the commonly used polymers, methacrylic acid and their ester copolymers known as Eudragit[®]; pH-sensitive polymers have been used for years in various formulations for coating, enteric coating, taste masking, or as therapeutic vehicles. Studies have shown that Eudragit improves the permeation of pharmaceutical active ingredients through skin, intestinal villi or cornea. Eudragit E100 and L100 in particular have been extensively studied for their ability of swelling/deswelling as a function of pH and salinity for coating. However, the possibility of preparing pH-sensitive particles from these polymers has not been systematically explored due to the difficulty of precipitating them as (nano)particles. Thus, the aim of this research work is to fully characterize these two Eudragit polymers and to study different ways of preparing Eudragit E100 and L100 (nano)particles in aqueous solution by precipitation process. In the first part of this work, we brought some clarifications on the solubility and precipitation domains of the two copolymers. We observed that a synergic action of the polymer concentration, the final pH of the medium as well as the incubation time influence the solubility of Eudragit E100 and L100 which is neglected in the state of the art. The titration of the two copolymers allowed us to determine the carboxylate and the amino content of respectively Eudragit L100 and Eudragit E100. In addition, the influence of various parameters such as pH, polymer content and ionic strength of the medium on both Eudragit precipitation was studied. In a second part, the influence of various secondary polymers on complexation and on the colloidal properties of Eudragit L100 and E100 particles was investigated. In this context, polyethylenimine was found to form a complex with Eudragit L100 and to stabilize the formed particles exhibiting submicrometric size with a narrow size distribution and high stability. In a third step, surfactants effect on the precipitation of Eudragit E100 and E100 was studied. This allowed us to identify the nature of polymer-surfactant interactions and the complexation mechanism of Eudragit E100 and Eudragit L100 as function of surfactant concentration.

Keywords : Eudragit, Precipitation, pH-sensitive polymers, Polyelectrolyte complexes (PECs), polyelectrolyte-surfactant complexes (PESCs).

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INTRODUCTION GENERALE

Les polymères (naturels ou synthétiques) sous leurs différentes formes connaissent de nos jours une utilisation intensive dans des secteurs d'activité tels que l'industrie automobile [1], l'électricité et l'électronique [2], le génie civil [3, 4, 5], l'agroalimentaire [6, 7, 8], l'industrie cosmétique et chimique [9, 10], les procédés de séparation [11, 12] ou encore l'industrie pharmaceutique et la médecine [13, 14, 15]. Dans l'industrie pharmaceutique notamment, de nombreux polymères sont employés pour l'encapsulation de molécules actives. Le choix des polymères est fonction de leurs caractéristiques et des applications visées pour les produits élaborés [16]. En effet, les polymères peuvent être employés à des fins de masquage de goût (molécules administrées par voie orale), de protection de substances actives dont ils assurent la biodisponibilité et une libération contrôlée en des sites spécifiques de l'organisme [17]. C'est sur cette aptitude que repose l'utilisation des polymères dans le traitement de diverses pathologies telles que le cancer [18], l'asthme [19, 20] et les maladies inflammatoires [21, 22]. Une catégorie de polymères appelés polymères pH-sensibles convient particulièrement pour l'atteinte des objectifs susmentionnés. Les polymères pH-sensibles sont des polymères qui répondent de diverses manières aux variations de pH dont fait l'objet le milieu dans lequel ils se trouvent. Cette réponse se traduit par la modification des propriétés des chaînes polymériques telles que la solubilité, la structure et la conformation des chaînes ou encore l'activité de surface [23]. Outre leur utilisation comme vecteur thérapeutique, les polymères pH-sensibles trouvent application dans des domaines divers et variés. Ils sont notamment employés dans la fonctionnalisation de surfaces et de membranes [24, 25, 26], comme capteurs et actionneurs [27], dans les techniques de séparation (extraction, chromatographie, électrophorèse) [28], comme agent stabilisant ou tensioactif dans l'industrie chimique [29], floculants [30, 31] ou fertilisants dans l'industrie agroalimentaire [32, 33].

Parmi les polymères pH-sensibles employés dans l'industrie pharmaceutique, une place importante est occupée par les copolymères d'acide méthacrylique et leurs esters connus sous le nom commercial d'Eudragit[®]. Il s'agit d'une façon générale de polymères synthétiques

anioniques ou cationiques d'acide méthacrylique, d'esters d'acide méthacrylique, de méthacrylate de diméthylaminoéthyl, le tout dans des ratios différents [17, 34]. La protection des principes actifs contre les enzymes et fluides gastriques par exemple ou encore la réduction de l'irritation gastro-intestinale causée par les anti-inflammatoires non-stéroïdiens peuvent en guise d'exemple être réalisées par le biais de ces polymères [35, 36]. Les Eudragit, sensibles au pH sont utilisés depuis de nombreuses années dans diverses formulations à des fins d'enrobage, de masquage de goût [37, 38], ou comme vecteurs thérapeutiques pour l'amélioration de la perméabilité à la peau [39, 40], aux villosités intestinales [41, 42] ou encore à la cornée de principes actifs pharmaceutiques [43, 44]. Ils servent en effet à la protection des principes actifs contre la dégradation due à la variation du pH le long du tractus gastro-intestinal afin d'en améliorer la biodisponibilité. Ils permettent de ce fait de cibler et d'atteindre différents organes spécifiques tels que l'estomac, le duodénum, le côlon ou encore les cellules épithéliales, la surface de la peau et les follicules pileux. En effet, les polymères sensibles au pH peuvent encapsuler des principes actifs pendant leur précipitation (sous forme particulière) et en assurer la libération pendant leur solubilisation. Les processus de précipitation et de solubilisation sont contrôlés par le pH du milieu. Les deux premières formes de ce polymère introduites en 1954 ont été les formes L et S pour le revêtement de comprimés à enrobage entérique. Ces polymères présentent l'avantage d'offrir des revêtements de meilleure qualité (comparaison faite avec d'autres matériaux) avec une désintégration rapide et une libération prolongée et contrôlée du principe actif encapsulé [17, 35]. Aujourd'hui, deux des Eudragit les plus utilisés sont les Eudragit E100 et L100. Le premier est soluble à pH acide et précipite en milieu basique. Les domaines de solubilité et de précipitation se trouvent inversés pour le second. C'est sur ces deux formes d'Eudragit que va porter l'étude rapportée dans le présent manuscrit.

Les Eudragit E100 (copolymère de diméthylaminoéthyl méthacrylate, butyle méthacrylate et de méthyl méthacrylate dans un rapport 2 :1 :1) et L100 (copolymère d'acide mé-

thacrylique et de méthyl méthacrylate dans un rapport 1 :1) ont été étudiés de manière approfondie pour leur caractère hydrophile/hydrophobe en fonction du pH et de la salinité pour l'enrobage [45, 35, 17, 34]. Toutefois, la possibilité de préparer des particules sensibles au pH à partir de ces polymères n'a pas été systématiquement explorée en raison de la difficulté résidant dans leur homo-précipitation (ou auto-précipitation) sans altération et/ou modification de leur structure chimique en milieu aqueux [46, 47]. Il est plus courant en effet de trouver dans la littérature des études où ces polymères sont utilisés pour l'encapsulation de principes actifs médicamenteux, d'huiles essentielles, de protéines ou d'acides nucléiques par précipitation (nanoprécipitation, coprécipitation) en milieu organique [48, 49, 50, 51].

La précipitation est une opération permettant de faire apparaître une phase solide insoluble pure à partir d'une solution d'un composé soluble par réaction chimique. Désignée bien souvent par cristallisation réactive, O. Sohnel et J. Garside y font référence comme étant la cristallisation de produits présentant une très faible solubilité [52], le solide obtenu pouvant être cristallin ou amorphe. Les différents mécanismes retrouvés au niveau de ces deux opérations présentent de grandes similarités et il est parfois difficile d'établir une réelle frontière entre elles. On retrouve en effet pour décrire ces opérations les mêmes notions fondamentales que sont la solubilité et la sursaturation ainsi que les mêmes mécanismes que sont la nucléation, étape où les nucléi apparaissent, la croissance où les nucléi grossissent ainsi que les modifications secondaires intervenant sur les cristaux/particules en formation (agglomération, brisure, attrition, mûrissement d'Ostwald) avec dans le cas de la précipitation quelques particularités liées à la cinétique de réaction chimique ou au mélange des réactifs. La précipitation est un mécanisme ayant lieu à une sursaturation très grande et qui fait intervenir de façon rapide et quasi simultanée une nucléation et la croissance des nucléi ainsi que plusieurs autres mécanismes secondaires que sont le mûrissement et l'agglomération. Dans ces conditions, la nucléation primaire est prépondérante et les particules sont très fines. D'autre part, ces fines particules sont sujettes au phénomène d'agglomération et les fortes interactions

particules-solvant conduisent à des suspensions d'aspect visqueux.

Ainsi, ce travail de thèse a pour objectif d'étudier différentes voies de préparation de particules d'Eudragit E100 et L100 en solution aqueuse par précipitation. Cette étude est subdivisée en deux grandes parties.

La première grande partie est dédiée à une revue bibliographique portant sur les matériaux stimulables. Elle présente notamment les différentes catégories de matériaux polymères stimulables à savoir les polymères, les nanogels et les membranes stimulables. L'utilisation des polymères stimulables comme matériau de revêtement est discutée. Les différents mécanismes mis en jeu au niveau de ces polymères en réponse à différents stimuli (pH, température, lumière, électricité, biologique) ainsi que les différents types de structures élaborés et leurs applications possibles y sont abordés. La partie bibliographique de ce manuscrit traite plus spécifiquement dans son deuxième volet des polymères pH-sensibles et leurs applications les plus récentes. Dans cette deuxième partie, nous nous sommes intéressés à une catégorie précise des polymères stimulables, à savoir les polymères pH-sensibles. Leurs caractéristiques principales sont présentées et une classification y est proposée. Y sont abordés également leur constitution, les méthodes de synthèse ainsi que les domaines d'applications. Les polymères sensibles à deux (2) ou plusieurs stimuli sont également abordés dans cette partie de la revue bibliographique.

La deuxième grande partie de ce manuscrit est consacrée au volet expérimental de ce projet de thèse. L'étude expérimentale comporte trois parties. La première partie est consacrée à l'étude des domaines de solubilité et de précipitation des deux copolymères Eudragit E100 et Eudragit L100. Ces domaines, approximatifs dans la littérature sont clarifiés au travers de notre étude. L'effet des paramètres que sont le pH, la salinité, la concentration en polymère ou en solution tampon et le temps d'incubation sur la solubilité et la précipitation des deux

copolymères est étudié. De plus, la titration des fonctions carboxylate et amine des deux copolymères est réalisée. La deuxième partie du volet expérimental est consacrée à l'étude de l'influence d'un polymère secondaire sur la précipitation directe par acidification ou basification des deux copolymères. L'influence de la présence de polyélectrolytes non chargés (alcool polyvinylique, dextran 40 et Pluronic F68) et de polyélectrolytes chargés (acide polyacrylique, polyéthylèneimine et amino-dextran) sur les propriétés colloïdales des particules d'Eudragit E100 et L100 est étudiée et discutée. Par ailleurs, la formation de complexes polyélectrolytiques impliquant ces deux formes d'Eudragit est discutée. Dans une troisième partie, la précipitation des Eudragit E100 et L100 induite par écrantage de charges est étudiée. Au travers de cette partie, la complexation des deux copolymères par des tensioactifs de charges opposées et la formation de complexes polymère-tensioactif est discutée. L'influence du pH et de la force ionique sur les complexes formés est abordée. Le but recherché est le contrôle des propriétés colloïdales des particules élaborées.

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PARTIE BIBLIOGRAPHIQUE

La première grande partie de ce manuscrit est consacrée à une étude bibliographique. Celle-ci se décline en deux volets. Ainsi, la première partie est consacrée aux matériaux stimulables de façon générale. La deuxième partie est plus spécifique aux polymères pH-sensibles. Cette étude bibliographique permet dans son ensemble de dresser un état de l'art sur les différents polymères naturels ou synthétiques découverts ou élaborés au fil des années et présentant une réponse caractéristique aux modifications de pH de leur milieu environnant. Les polymères pH-sensibles rencontrés sont identifiés au travers de ce travail de même que leurs potentialités pour diverses applications. Les applications les plus récentes qui en découlent sont également présentées.

Cette étude bibliographique permet de constater que les matériaux stimulables en général et les polymères pH-sensibles en particulier occupent une place non négligeable dans la vie de tous les jours à la vue des divers domaines d'applications. S'agissant des polymères pH-sensibles, ceux-ci sont utilisés dans l'industrie pharmaceutique principalement comme vecteurs de principes actifs médicamenteux. Outre les formules ayant fait leurs preuves et déjà commercialisées, de nombreuses études continuent de montrer leurs potentialités dans ce domaine avec des améliorations et spécifications croissantes.

Les polymères pH-sensibles qui nous ont intéressés tout particulièrement sont les copolymères Eudragit E100 et Eudragit L100. Nous avons pu constater qu'au-delà de leur grande utilisation comme agent de masquage de goût ou d'odeur ou comme matériau de revêtement entérique, ils souffrent d'un certain manque de données précises dans la littérature. Un des premiers points ayant attiré notre attention concerne les conditions précises de solubilité et de précipitation. Dans le but de préparer des particules pH-sensibles, ces données sont d'une importance capitale. Elles constituent en effet le point de départ du travail expérimental que nous nous proposons de réaliser.

Chapitre 1

LES POLYMERES STIMULABLES COMME MATERIAUX D'ENROBAGE

Étude bibliographique publiée sous la forme d'un
chapitre d'ouvrage : “*Polymer Coatings : Technologies
and Applications*”

Eds : Dr.Jyotishkumar Parameswaranpillai (Thailand),
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Cette première partie bibliographique est consacrée aux matériaux polymères stimulables [1]. Ces matériaux sont caractérisés par leur aptitude à réagir de façon réversible aux stimuli de leur milieu environnant. La réaction à ces stimuli se traduit par des modifications de leurs propriétés physiques et/ou chimiques [2, 3, 4]. Les stimuli peuvent être aussi bien d'origine physique (température, lumière, électricité) que chimique (pH, force ionique, potentiel redox) ou biologique (enzyme, antigène) [5, 6]. Dans cette revue bibliographique, quelques-uns des matériaux stimulables les plus importants sont abordés ainsi que les diverses applications dont ils font l'objet. Une attention particulière est accordée à leur utilisation comme matériau d'enrobage.

Cette revue bibliographique est scindée en trois parties. Dans la première partie, nous abordons entre autres les polymères, les nanogels et les membranes sensibles aux stimuli. Une définition de ces différents concepts est proposée. Leurs caractéristiques les plus importantes sont présentées ainsi que leurs principaux domaines d'application avec leurs avantages et quelques exemples. Dans la deuxième partie de ce travail, une attention particulière est portée sur les polymères stimulables et leur utilisation comme outil d'enrobage. L'utilisation à cette fin de polymères sensibles au pH, à la lumière, aux molécules biologiques, à la température ou encore à l'électricité y est traitée. Ces polymères sont en effet utilisés de façon intense dans l'enrobage (encapsulation) de molécules actives pour leur transport, leur libération ciblée et contrôlée [7, 8, 9] et aussi dans la mise au point de dispositifs médicaux tels que les organes artificiels [10, 11, 12]. De plus, des études ont montré leur aptitude comme bactéricides [13, 14] dans le revêtement textile en réponse à des enzymes spécifiques. La troisième partie de cette revue est consacrée à ces diverses autres applications des matériaux polymères stimulables. Leur utilisation sous diverses formulations notamment dans l'agriculture [15, 16, 17] et l'industrie agro-alimentaire [18, 19, 20], l'industrie cosmétique [21] etc. y est abordée.

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STIMULI-RESPONSIVE POLYMER COATINGS

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Abstract :

Stimuli-responsive polymers are an important branch of polymer science. Their ability to react to external stimuli in a reversible manner makes them a tempting target in several applications. As these polymers respond to stimuli such as pH, light, biological elements, temperature, and electricity, they can be used as coating layers on different types of materials in order to add more flexible properties. The stimuli-responsive polymers are used in food industry, agriculture, biomedicine, cosmetics, drug delivery, textile industry, and many more. In this chapter, some of the most important stimuli-responsive polymers are discussed and their recent applications in several fields are highlighted.

Keywords : Stimuli Responsive, Polymers, Nanogels, Membranes, Application.

1.1 Introduction

Polymers are used in most of the goods we use in our daily life, and they even form important parts of our own body, such as DNA and proteins. Since long time, polymers have been used in order to improve the quality of life. However, the real nature of the polymeric materials (natural rubber) was not known. Thanks to the economic dynamism of rubber industry in the 19th and 20th centuries, more investments were made to know about the behavior of rubber. This event made the intense debate among researchers in this re-

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gard. Therefore, they made many efforts and developed certain polymers suitable for almost every imaginable application. This foundational study caused the development of a new category of polymers that respond to their environment by changing their physical and chemical properties. Stimuli-responsive polymers are the materials that can react by altering their properties once subjected to external stimulus. Stimuli-responsive polymers are classified into different classes based on various criteria. For instance, stimuli-responsive polymers are divided into categories of thermal-induced, light-induced, electro-responsive, pH-responsive, and magnetic-responsive polymers (Figure 1.1). Based on the nature of cross-links, stimuli-responsive polymers are classified into chemically or physically cross-linked polymers. Biodegradable stimuli-responsive polymers are also nominated as a category. According to the switching segments' nature, stimuli-responsive polymers are categorized into T_g -type stimuli-responsive polymers with amorphous switching segment and T_m -type stimuli-responsive polymers with crystalline switching segment [1]. Stimuli-responsive polymer coatings continue to be used in evermore increasingly diverse applications and sectors such as food, agriculture, drug delivery, biomedical diagnostics, sensors, textiles, and cosmetics [2].

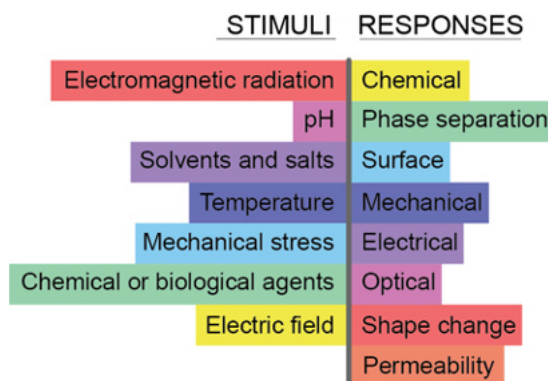


FIGURE 1.1 – Synthetic polymers' possible stimuli and responses.

In this chapter, we highlight some of the structures made from stimuli-responsive materials. We discuss different stimulus mechanisms, and we shed light on some important applications of that technology.

1.2 Stimuli-Responsive Materials

1.2.1 Stimuli-Responsive Polymers (SRP)

Stimuli-responsive polymers, also known as smart or intelligent or environmentally sensitive polymers, are materials that constitute an important class of polymers today. They can react to small external changes in their immediate environment by displaying significant reversible [3, 4], large, microstructural, physiological, and physicochemical changes in their properties [5, 6]. One of their fundamental characteristics is that they return to their initial state as soon as the stimuli responsible for the modification in their physicochemical properties are removed [7].

Stimuli-responsive polymers can be of either natural or synthetic origin. Among natural responsive polymers, chitosan and albumin are capable of showing thermo- and pH-responsive properties [8, 9, 10]. Moreover, methylcellulose and gelatin can be mentioned with thermo-responsive properties [11]. Synthetic stimuli-responsive systems containing polymers can be designed either with a responsive polymer, or by combining a polymer with a responsive compound, the polymer serving only as a template/carrier for that compound [12]. Stimuli-responsive polymers are synthesized using polymerization techniques such as living anionic and cationic polymerization, controlled radical polymerization, atom transfer radical polymerization, and reversible addition–fragmentation chain-transfer polymerization [13]. In the build-up of synthetic stimuli-responsive polymers, functional groups that make effective response to stimuli (charge, polarity, and solvency, for instance) are incorporated along a polymer backbone [14], resulting in abrupt and clear changes in macroscopic material properties. Response to stimuli can be defined in various ways. These responses may be associated with modifications in individual polymer chain dimensions or size, shape, surface characteristics, secondary structure, solubility, and/or intermolecular association degree. In most cases, the formation or destruction of secondary forces (hydrogen bonding, hydrophobic effects, elec-

trostatic interactions, etc.), simple reactions (e.g., acid–base reactions) of moieties linked to the polymer backbone, and/or osmotic pressure differences are responsible for this response. Dramatic alterations in the polymeric structure, such as degradation of polymers upon the application of a specific stimulus by bond breakage in the polymer backbone or at pendant cross-linking groups, can also be mentioned as a response of a stimuli-sensitive polymer to stimuli [15].

External stimuli that provoke these changes can be divided into three main groups : physical stimuli (mechanical stress, electric, magnetic, ultrasound, light, temperature), chemical stimuli (electrochemical, pH, ionic strength), and biological stimuli (enzyme and/or biomolecules) [16, 17]. Dual-stimuli-responsive polymers can be also mentioned as polymers that simultaneously respond to more than one stimulus. It should be taken into consideration that stimuli may also occur internally. The well-known examples of this case that is applied in drug delivery systems include changes in pH that occur in certain organs or diseased states, changes in temperature, the presence of specific enzymes, antigens in the human body [18], or changes in physiological conditions [19, 20].

Based on their physical properties, stimuli-responsive polymers are classified into three categories :

- *Linear free polymer chains in solution* : They respond to stimuli that induce a reduction in the number of hydrogen bonds between polymer and water or the neutralization of electrical charges. Linear free soluble polymer chains precipitate with the increasing hydrophobicity. Polymers exhibiting this property have applications in bioseparation of proteins, cells, and other bioparticles.
- *Covalently cross-linked reversible and physical gels* : Hydrogels that swell in aqueous media may respond rapidly to small changes in pH, temperature, light intensity, ionic

strength, magnetism, inflammation, ultrasound, electrical fields, or biochemicals. Smart polymer hydrogels find applications in microfluidics, actuators, and sensors.

- *Smart surfaces or membranes* : Polymer chains that have the ability to undergo changes under specific stimuli conditions when adsorbed or grafted to surfaces are classified under this category. Indeed, the surfaces can be converted from hydrophilic to hydrophobic as well. Thus, surface is hydrophilic when the polymer is in its soluble state and hydrophobic when insoluble due to the action of stimuli. Separation of substances that interact differently with hydrophobic matrices can be mentioned as a potential application. Smart surfaces find applications in tissue engineering (generation/repair) and temperature-controlled or porosity-controlled separation [18, 19, 20, 21].

The rise in interest that has characterized stimuli-responsive polymers in these last decades is related to the various possibilities brought to polymer science and the different promising applications associated with them. In fact, in addition to the applications mentioned above, stimuli-responsive polymers are used in drug delivery [22, 23], smart coating, intelligent medical instruments and auxiliaries, artificial muscles and robotics [13], smart textiles and apparel [1, 24], biomimetic devices, electrochemical devices, and microelectromechanical systems. Furthermore, SRP coating was used to fabricate structured particles that can range from nanoscale to microscale. By adding this responsive layer, particles can undergo modification in their structure, dimensions, and interactions, when introduced to an external stimulus. Several structured particles can be synthesized in this fashion, such as core-shell particles, micro-/nanospheres, micro-/nanogels, and nanocomposites (Figure 1.2), and can be used in various technical and biomedical applications. In fact, using such a technology, mimicking a living cell can theoretically be done by combining several compartments that can communicate, exchange energy, and perform mechanical work in a single particulate structure [25].

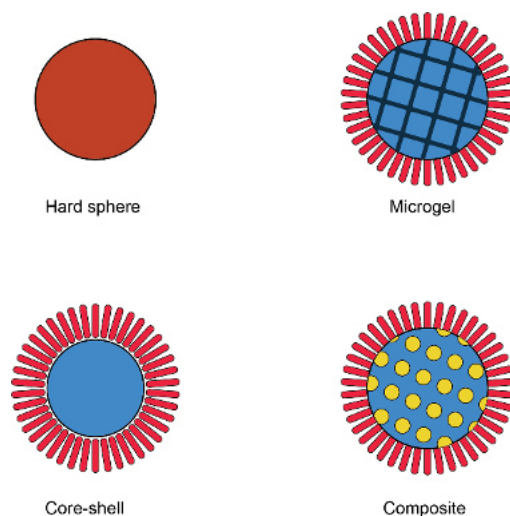


FIGURE 1.2 – Some of the particulate morphologies.

1.2.2 Stimuli-Responsive Nanogels

Polymer nanogels are a special kind of nanomaterials since they combine the properties of nanoparticles and hydrogels. Basically, polymer nanogels are cross-linked colloidal particles formulated by swelling caused by the adsorption of large amounts of solvent. As a result, polymer nanogels are soft nanoparticles, thanks to the fluctuation of the high solvent content. However, their cross-linked three-dimensional polymeric network renders these particles resistant to dissolution [26, 27]. Different materials were used to prepare polymer nanogels such as poly(*N*-isopropylacrylamide), polyethylene glycol, polypeptide, and chitosan [28].

The properties of stimuli-responsive nanogels (SRN) make them a good candidate for biomedical and drug delivery applications. Mainly, being sensitive to environmental stimuli allows a better control of drug release. In addition, due to their interior cross-linked network, drug loading is much higher and drug leakage is much lower in the case of nanogels compared to other nanocarriers [29]. Moreover, polymer nanogels possess a stable 3D structure promoting a stable desired size that is needed for passive drug delivery through the enhancement of permeation and retention effect. SRN were also used for active tumor targeting due to their ease of functionalization of polymer units [28]. Additionally, SRN can encapsulate mul-

tiple drugs with different solubility profiles. Jin et al. developed a triple-stimuli-responsive (protease/redox/pH) biodegradable PEGylated P(MAA/BACy) nanogel as a carrier for both hydrophilic doxorubicin and hydrophobic paclitaxel [30]. It was found that the double-drug-loaded system possesses favorable targeting ability and therapeutic effect, lower biotoxicity, longer in vivo circulation time, enhanced drug release profile, and a safe biodegradation [31]. These results show the validity of complex nanogel structures as drug vehicles. In fact, core-shell nanogel structures with constrained swelling to one layer were also suggested as a strategy to control multi-drug loading with desired amounts [32].

SRN are also known for their ease of synthesis. Basically, two main approaches can be used for the preparation of SRN (self-assembly of polymers, or polymerization in a heterogeneous environment). In both cases, cross-linking is an important step to ensure the colloidal stability of the nanogels. The polymerization method is usually done by emulsion polymerization, or inverse emulsion polymerization depending on the chosen continuous phase [28]. PEO-block-P(oligo(ethylene glycol) monomethyl ether methacrylate) particles were synthesized by atom transfer radical polymerization and cross-linked via inverse miniemulsion using a disulphide functionalized cross-linker. The cross-linked nanogels showed an excellent colloidal stability and controllable swelling ratio [33]. On the other hand, self-assembly of polymers is based on the formation of micelles, followed by a non-covalent interaction between the chains and cross-linking [34]. Cholesterol-bearing xyloglucan molecules were self-assembled in water forming nanogels. Cholesterol was used as a physical cross-linking point. It was found that the obtained nanogel can successfully be coupled with hydrophobic molecules with low molecular weight, and by incorporating galactose into their surface, they can be specifically internalized into hepatocytes, making them a good drug carrier candidate [35]. As stated before, cross-linking is a crucial step in the preparation of SRN. Different types of cross-linking can be used, such as physical cross-linking, in which the interaction between polymer moieties is done through different driving forces : hydrophobic interactions [35],

electrostatic interactions, and host–guest interactions [36]. The other cross-linking strategies are disulphide-based, amine-based, click chemistry-based, and photo-induced cross-linking [28].

1.2.3 Stimuli-Responsive Membranes

Nowadays, membrane technology has widely been used in numerous applications such as drug delivery system [37], chemical separation [38], and water desalination [39], due to its remarkable properties with less energy consumption. Specifically, stimuli-responsive membranes (SRM) have gained much attention in the past decades due to the fact that they could change their physicochemical properties in response to a change in the environment stimuli [40]. SRM could be potentially designed to a system that responds to the changes in external stimuli : pH, temperature, ionic strength, light, and electric or magnetic field [38]. Functional materials (such as polymers, nanogels, and nanoparticles) with reversibly switchable physicochemical properties are generally considered as crucial resources for the preparation of SRM to provide different responsive properties. Husson et al. [41] used a two-step process to well explain the responsive mechanisms of SRM. Firstly, changes in the external environment cause a specific conformation transition of a responsive functional material, and then these conformational transitions to some extent are easy to detect through naked eye or other simple technology methods. In fact, they always react to environmental stimuli to some extent by changing their conformation/polarity along the backbone, side chains, segments, or end groups. As a result, making alterations to the polymer chain length, chemical composition, architecture, and topography is the conventional method to optimize the responsive properties of SRM. There are two essential methods used to prepare SRM : (i) blending of different stimuli-responsive polymers to manufacture membranes and (ii) modification of existing membranes through grafting of stimuli-responsive polymers [42]. The former is a crucial method in the design of porous SRM. By taking this approach, the targeted mechanical properties, pore structure (porosity, pore size, and pore size distribution), and barrier structure (symmetric

and asymmetric) can be obtained. Various membrane processing techniques, such as solvent casting, phase inversion, and interpenetrating polymer networks, have been applied to develop SRM. Modification of the existing membranes is also an important method to prepare SRM, and the membrane performance is enhanced through the addition of functional materials. This method enables responsive properties on the membrane surface and keeps the useful properties of the original membrane. Numerous polymer coating techniques, namely physical adsorption, chemical grafting, coating, layer-by-layer (LBL) assembly, chemical vapor deposition, have been used to modify the chemical surface or pores of the membranes [43].

1.3 Stimuli-responsive polymers in Coating Technology

1.3.1 pH-sensitive polymers

pH-sensitive polymers are a group of stimuli-responsive polymers that can respond to environment pH through structural and property changes such as surface activity, chain, conformation, solubility, and configuration [44]. Materials referred to as pH-responsive polymers present the property to have potential ionizable groups in their structure. These groups are weak acidic or basic moieties sensible to pH variations and confer the pH sensitivity to the overall molecule [4]. Sensitivity to pH in response to environmental pH modification is made through the acceptance or the release of protons leading to conformational changes and changes in the colloidal behavior of the polymer, such as flocculation, chain collapse or extension, and/or precipitation of homopolymers [44, 45]. pH-responsive polymers can be produced using different polymerization techniques. Emulsion polymerization is the technique used for the preparation of most of the pH-responsive polymers due to the well-controlled size distribution. Moreover, anionic polymerization, group transfer polymerization, stable free radical polymerization, atom transfer radical polymerization, atom transfer radical polymerization, and reversible addition–fragmentation chain-transfer polymerization are other polymeriza-

tion techniques used for the preparation of pH-responsive polymers [46].

According to their origin, natural pH-responsive polymers can be distinguished from synthetic ones. Among natural pH-responsive polymers, the most studied and used ones are dextran, gelatin, albumin, chitosan, hyaluronic acid, and alginic acid [11]. For synthetic pH-responsive polymers, two main categories can be identified : polymers with acidic group and polymers with basic group. Table 1.1 lists some of the basic polymers used as pH-sensitive polymers or moieties in the build-up of what is known as block pH-sensitive polymers.

Indeed, according to their structure, pH-sensitive polymers can be classified as linear homopolymer, copolymer (hydrophilic or amphiphilic block (di-, tri-, multi-block copolymers)), pH-responsive star polymers (with linear polymer chains connected to a central core), pH-responsive branched and hyper-branched polymers, pH-responsive dendrimer polymers, and pH-responsive brush and comb polymers [44].

Development of performant techniques has allowed the preparation of well-defined block copolymers that exhibit self-assembly behavior to external pH modification. pH-responsive block polymers can exhibit different sorts of responses following a pH modification. Thus, self-assembly such as formation of micelles, unimers, gels, vesicles, swelling, and deswelling can be noticed in the case of block copolymers [47, 48].

pH-responsive polymers find application mainly in drug delivery since they are used as a coating material in controlled drug release systems or as drug carriers. Changes in pH in the gastrointestinal tract (acidic in stomach and basic in intestine) [18] and the biocompatibility of the pH-sensitive polymers make them ideal candidates for specific human drug delivery since they are able to switch from swelling to deswelling state in response to local body pH. By this process, they are capable of retaining or release drugs in specific sites or organs

according to pH. For this purpose, polymethacrylate, synthetic anionic or cationic copolymers of acrylic acid, methacrylic acid, (dimethyl amino) ethyl methacrylate, methacrylic acid esters are known under the commercial name of Eudragit that are largely used as a coating material for the encapsulation of active ingredients and deliverance in specific site of human body [49]. Moreover, pH-responsive polymers find application in gene delivery and are also used in drug delivery to cancer tissues towards micelles' encapsulation using pH differences between extracellular pH of normal tissues and tumor extracellular pH [50, 51, 52].

Acidic polymers	Poly(ethyleneglycol acrylate phosphate) (PEGAP)	Polyacrylic acid (PAAc)
	Poly(vinylphosphonic acid) (PVPA)	Poly(methacrylic acid) (PMMAc)
	Poly(ethylene glycol methacrylate phosphate) (PEGMP)	Poly(propylacrylic acid) (PPAAc)
	Poly(4-vinyl-benzyl phosphonic acid) (PVBPA)	Poly(4-vinylbenzoic acid) (PVBA)
	Poly(vinylsulphonic acid) (PVSA)	Poly(itaconic acid) (PIA)
	Poly(4-styrenesulphonic acid) (PSSA)	
	Poly(2-acrylamido-2-methylpropane sulphonic acid) (PAMPS)	
	Poly(2-acrylamido-3-sulphopropyl methacrylate potassium salt) (PKSPMA)	
	Polyaspartic acid (PASA)	
	Poly(L-glutamic acid) (PGA)	
Basic polymers	Poly(histidine) (PHIS)	
	Poly(vinylphenylboronic acid) (PVPBA)	
	Poly(3-acrylamidophenylboronic acid) (PAAPBA)	
	Poly(2-dimethylamino)ethyl methacrylate (PDMA)	
	Poly(2-diethylamino)ethyl methacrylate (PDEA)	
	Poly(2-dipropylamino)ethyl methacrylate (PDPAEMA)	
	Poly(2-diisopropylamino)ethyl methacrylate (PDIPA)	
	Poly(<i>N</i> -(3-dimethylamino)-propyl) methacrylamide (PDMAPMAm)	
	Poly((2-dimethylamino)ethyl acrylate) (PDMAEA)	
	Poly(2- <i>ter</i> -butylamino)ethyl methacrylate (P <i>t</i> BAEMA)	
Poly(<i>N,N</i> -dialkylvinylbenzylamine)		
Poly(2-diethylamino)ethyl acrylamide (PDEAm)		
Poly(2- <i>N</i> -morpholino)ethyl methacrylate (PMEMA)		
Polyacrylomorpholine (PAM)		
Poly(2- <i>N</i> -morpholino)ethylmethacrylamide (PMEMAm)		
Poly(<i>N</i> -ethylpyrrolidine methacrylate) (PEPyM)		
Poly(<i>N</i> -acrylo- <i>N'</i> -alkenyl piperazine)		
Poly(4-vinylpyridine) (P4VP)		
Poly(2-vinylpyridine) (P2VP)		
Poly(<i>N</i> -vinylimidazole) (PVI)		
Poly(6-(1- <i>H</i> -imidazol-1-yl)hexyl-methacrylate (PImHeMA)		
Poly(propyleneimine) dendrimer (PPI)		
Poly(ethyleneimine) dendrimer (PEI)		
Poly(amidoamine) dendrimer (PAMAM)		

TABLE 1.1 – Classification of Basic Acidic and Basic pH Responsive Polymers [44]

1.3.2 Light-sensitive polymers

Light-responsive polymers are photodeformable in response to light stimuli. The advantage of using such materials in coating technology lies in the simplicity of operation, the avoidance of using chemical reactants and therefore limiting chemical contamination, and scalable miniaturization [53]. In addition, light sensitivity offers a remote application, ease of dosing, and accurate positioning and resolution of the response [54].

For a polymer to become light responsive, a chromophore (photoresponse functional group) should be incorporated into the polymer chain. Two categories of chromophores can be found, reversible and irreversible. Reversible chromophores, upon light excitation at a specific wavelength, undertake a reversible isomerization. This allows the alteration of the properties of the host polymer by irradiation at two different wavelengths. This reversible isomerization is important in different applications such as information storage and artificial muscles [55, 56]. Spiropyran, an organic molecule that upon light excitation is engaged in a photocleavage of a spiro C-O bond, was used to prepare photochromic polymer brushes. Dense and smooth polymer films were successfully prepared and used as surfaces with switchable color and wettability by light stimulation. A specific wavelength can convert a non-polar spirocyan to a polar one, and it can be reverted to its non-polar state using visible light [57].

On the other hand, irreversible chromophore is subject to unreversed changes upon light excitation. Therefore, equilibrium between two states does not exist. This will give the advantage of 100% photoconversion, which makes them ideal for drug delivery since this irreversibility can lead to effective drug release and better degradation when required [54]. This strategy was used in laser-induced forward transfer method (LIFT), in which biological molecules, such as protein and DNA, and even living organisms (cells) can be coated with a sacrificial polymer layer, and upon laser pulse emission, the coated molecule can be shifted

from the polymer substrate to a receiver substrate in close proximity [58]. Doraiswamy et al. were able to transfer mammalian cells using polytriazines as sacrificial polymer that also acts as an irreversible chromophore [59]. Another approach was the coating of silica nanoparticles with NIR-light-responsive polymer via self-assembly. Due to the presence of coumarin moieties in the polymer, it can be disrupted by excitation by a femtosecond NIR light laser (800 nm) via a two-photon absorption process. It was found that under excitation with such light, the core-shell structure of the non-vehicle was able to release the pre-loaded drug in a controllable manner. In addition, in vitro results show a successful targeting of tumor cells once decorated with folic acid [60]. NIR range is considered more desirable for drug delivery than UV or visible light since it offers deep penetration without harming body tissues; however, most of the light-sensitive systems were tested in vitro and in vivo applications still require further development.

1.3.3 Biological Environment-sensitive polymers

Smart polymers that respond to physical and chemical stimuli such as light, pH, or temperature are desired because they are well controlled and easily measured. These polymers can be stimulated externally, offering a good control of the material properties. However, when it comes to biological systems, it is more complex and challenging. A temperature-responsive polymer, for example, cannot be targeted towards a specific receiver. Therefore, more targeted responsive systems are necessary [61].

Polymers responsive to biological environment are used for living organisms and applied in drug delivery, biomedicine, and cell engineering [62]. They can be enzyme responsive, ligand responsive, cell responsive, or generally responsive to biochemical environments. For example, responsiveness to reactive oxygen species (ROS) at the inflammation site of tumors can be exploited for targeted drug delivery by drug-loaded responsive polymer nanoparticles [63]. Doxorubicin-loaded ROS-responsive polymeric micelles were developed by Sun et al. as

antitumor agents by introducing ROS-responsive thioketal as a linker between poly(ethylene glycol) and poly(ϵ -caprolactone). In a ROS-rich environment, the surface of these micelles is degraded, and the drug was specifically released allowing a better in vitro anticancer activity of doxorubicin [64]. Other ROS-responsive moieties were also used for such applications, such as boronic ester and sulphide groups. However, few challenges still exist. The levels of ROS can vary from patient to patient, and therefore, these formulations must be personalized for each patient. In addition, the biocompatibility of the used linkers and their stability during circulation in normal cell environment should be addressed [65].

Enzyme-responsive polymers are another promising approach. These polymers have the advantages of being biocompatible, since enzymatic stimuli occurs naturally, and lead to more accurate targeting for the drug and therefore lead to a higher therapeutic efficiency and lower side effects [61]. Due to these advantages, enzyme-responsive polymers were applied as cell supports, injectable scaffolds, and drug delivery systems. Huang et al. used casein (a natural milk protein) as a coat for iron oxide nanoparticles. This system was loaded with doxorubicin as a model drug. It was found that these particles were stable in the acidic gastric environment in the presence of gastric protease. However, the outer casein layer was degraded in the presence of intestinal protease, allowing the maintenance of the drug's bioactivity and the enhancement of the drug delivery efficiency [66]. Synthetic polymers can also be used as enzyme-responsive drug delivery systems by introducing an enzyme-sensitive cross-linker to their matrix, rendering the polymeric structure a target to degradation by protease. Polystyrene nanoparticles were prepared by inverse miniemulsion and cross-linked with a hydrophobic peptide as a trypsin substrate. This formulation can have a promising future in nanomedicine, in vitro detection of specific enzymes, and cancer therapy [67]. Another example of enzyme-responsive polymers is nanoparticles sensitive to protein kinases. Nanoparticles comprising hydrophobically modified peptide substrate of a protein kinase were prepared for monitoring the activity of the latter by exploiting the enzyme to change the

electrostatic interaction of the polymer aggregates in the particle [68].

Biological environment-responsive polymers were also applied as smart coatings for textiles developed as antibacterial vectors and used in several applications such as bedding and wound dressing. Kratochvil et al. developed a non-woven polymer nanofiber coating loaded with macrocyclic peptide 1, a potent non-bactericidal quorum-sensing inhibitor in *S. aureus*. The peptide was loaded to the nanofiber by electrospinning and was able to inhibit the production of bacterial hemolysins (a quorum sensing controlled virulence phenotype) and reduce the lysis of erythrocytes [69]. The release of the antimicrobial agent was in response to pathogenic bacteria specifically, and it did not respond to non-pathogenic strains. This approach can be a great alternative to antibiotic-dependent therapy, especially with the growing antibiotic resistance of *S. aureus* [70].

1.3.4 Temperature-sensitive polymers

Temperature-sensitive polymers (TSP) are sensitive to the temperature and alter their microstructural characteristics in response to the degree of temperature change. Temperature-sensitive polymers are well known and are the most employed polymers in drug delivery and biomaterials. Indeed, a small change in temperature is able to make new adjustments in TPS because they have a very sensitive balance between the hydrophobic and hydrophilic groups [71]. The critical solution temperature is an important property of such kind of polymers. The polymer will become insoluble after heating, if the polymer solution has a phase lower than the critical solution temperature; i.e., it has one lower critical solution temperature (LCST). The interaction strengths (hydrogen linkages) between the polymer and water molecules become inconvenient above the critical solution temperature and cause polymer swelling because of its dehydration and occurrence of hydrophobic interaction predominance [72].

The LSCT is the critical temperature at which the polymeric solution separates into two phases, going from one phase (isotropic state) to two phases (anisotropic state). LCST changes due to hydrophilic or hydrophobic incorporation existence within a polymeric system. The phase transition occurrence that causes a change in polymer is easily observable in certain temperatures.

TSP were mainly used in biomedical applications where the selected TSP should be biocompatible and non-immunogenic. To design an effective platform, it is crucial to understand the molecular mechanism behind the performance of TSP [73].

1.3.5 Electrical-sensitive polymers

Electrical-responsive polymers have the ability to deform (shrinking, swelling, bending) in response to an external electric field. In other words, they have the ability to transform electrical input into mechanical output. For this reason, electro-responsive polymers found their way to biomechanical applications, artificial muscles, sensing, chemical separation, and drug delivery [15].

The most researched form of electro-responsive polymers is polyelectrolyte hydrogels. In the presence of an electrical field, the ionic groups inside the gel get pushed to the anode side, which leads to swelling, or to the cathode side, which leads to shrinking and ultimately leads to a reversible deformation and volume change of the gel. Neutral polymers can also be affected by electric field; many polymer gels have been found to be subject to swelling via electrostriction (change in the length of materials in the presence of an external electric field). In addition, neutral materials can acquire a translational motion when introduced inside a non-uniform electric field via dielectrophoretic effect [74]. Both natural and synthetic polymers were used to prepare electro-responsive hydrogels, such as chitosan, chondroitin sulphate, hyaluronic acid, allylamine, and acrylonitrile.

Electrical-sensitive polymers have been studied in the development of artificial muscles. Many polymers were used in that context, but perhaps the most interesting one is polyacrylamide. This is due to several reasons : It is cheap, is easy to manipulate, is biocompatible, and have the same properties as living tissues. Moschou et al. developed an artificial muscle material based on an acrylic acid/acrylamide hydrogel blended with a conductive polypyrrole/carbon black composite. It was found that under electroactuation with a 1-volt voltage, the material showed a relatively fast response of 5 seconds and reversible bending in a neutral pH. In addition, the artificial muscle was incorporated into a bio-microelectromechanical system by immersing it in a 0.15 M NaCl solution and placing it above the polydimethylsiloxane membrane-covered micro-reservoir. It was found that under electroactuation, the bent hydrogel was able to push the membrane surface and pump the fluid from the reservoir into a calibrated microchannel with a low power consumption [75].

Electro-responsive polymers were also used in drug delivery. Kagatani et al. were able to produce poly(dimethyl amino propyl acrylamide) gel loaded with insulin. This gel was administered subcutaneously in rats, and by stimulation with an external constant current of 1 mA, a pulsatile decrease in plasma glucose level was observed. The release is caused by the electrokinetic flow of dissolved insulin with the water from the gel, explained by electrophoresis of the counterions and electro-osmosis of water molecules in the cross-linked polyelectrolyte gel network [76].

1.4 Applications of Stimuli-responsive materials

Due to their reversible responsiveness to environmental stimulus, stimuli-responsive polymer coatings were used in several applications. In this part, we will highlight some of these applications, the concept of their use, and recent advancements in their respective field. In

addition, some of the recent applications are summarized in Table 1.2.

1.4.1 Food

Stimuli-responsive polymer systems have proven to be an efficient tool to use in food-packing systems with a great potential to improve the safety, quality, and traceability of food products, as well as its convenience for consumers [97]. In addition, stimuli-responsive polymers were used in some functional food as coating materials for particle [98] or emulsion [99].

It is a well-established food quality control that is an essential research target to protect consumers against food-borne infection and to maximize the benefits of the food industries. Recent developments in smart food packaging to monitor the changes in the condition of food have attracted much attention. This technology may be incorporated in packaging materials or attached to the inside or outside of a package and aims to sense and share more information about food quality to consumer or producer during transport and storage [100]. Stimuli-responsive polymers have been regarded as a useful method to acquire packaging with responsive properties. For instance, a smart packaging system can be used to observe the distinct pH of foods with visual colorimetric changes of pH-responsive polymers inside the smart package [101]. In addition, packaging with responsive properties includes the sensors, which would detect the temperature, gas formation, microbial growth, freshness, and so on [97]. Principally, for food applications, the material used for packaging should have the 'Generally Regarded As Safe (GRAS)' status. Thus, most of the stimuli-responsive materials that can be used in actual food packaging have very limited implementation. Rather, natural polymers are promising materials in the design of smart packaging due to their compatibility and non-toxic nature on administration. Exploiting the pH-tunable ability of chitosan, Maciel, Yoshida, and Franco [77] established a prototype of a colorimetric temperature indicator for monitoring food quality. Liu et al. [78] developed a simple yet reversible pH-responsive chitosan-based emulsion system by exploiting the pH-tunable ability of chitosan. Based on

Application	Polymer	Responsiveness	Formulation	References
Food	Chitosan	pH and temperature	Colorimetric temperature indicator for monitoring food quality	[77]
	Chitosan	pH	Chitosan-based emulsion system	[78]
	Polyaniline	Microbial breakdown products	Films	[79]
	Polymers	Oxygen	Oxygen-scavenging film	[80]
	Phosphorescent Pt-porphyrin	CO ₂	Sensors	[81]
Agriculture	Carboxymethyl chitosan	Glutathione	-	[82]
	Attapulgate-NH ₄ HCO ₃ -glyphosate/amino silicone oil-poly(vinyl alcohol)	Temperature	Core-shell nanocomposites	[83]
	Hydroxypropyl methylcellulose	Environment	Hydrogels	[84]
<i>In vitro</i> biomedical diagnostics	Antibody-bound poly(<i>N</i> -isopropyl acrylamide)	Biomarkers	Polymer-coated gold nanoparticles	[85]
Sensors	Poly(<i>N</i> -isopropyl acrylamide)	Temperature and salt	Coated nanoparticles	[86]
	Poly(<i>N</i> -(3-amidino)-aniline)	CO ₂	Coated nanoparticles	[87]
	Chitosan (CHI)/poly(acrylic acid)	Ionic strength	Coated long-period gratings	[88]
	Poly(vinyl alcohol)	Glucose	Coated platinum electrode	[89]
Drug delivery	Ethylcellulose	pH	Polymer-coated insulin-loaded intestinal patches	[90]
	Eudragit [®] S100 and Eudragit [®] L100-55	pH	Polymer-coated insulin-loaded nanoparticles	[91]
	Ethylcellulose	Light	Polymer-coated insulin-loaded gold nanoparticles	[92]
	Poly(<i>N</i> -isopropylacrylamide- <i>co</i> - <i>N,N</i> -dimethylacrylamide)	Temperature	Core-shell nanoparticles	[93]
	Poly- <i>N</i> -isopropylacrylamide- <i>co</i> -itaconic acid	Temperature and pH	Doxorubicin-loaded core-shell nanoparticles	[94]
Cosmetics	Polyoxyethylene and polyoxypropylene	Temperature	Aqueous composition	[95]
Textile	Polyurethanes	Temperature	Polymer-coated shape-memory fabric	[96]

TABLE 1.2 – Applications of Stimuli-Responsive Polymers.

polyaniline film, Bambang et al. [79] developed a novel colorimetric food package label as a chemical sensor for real-time monitoring of the microbial breakdown products in the head-space of packaged fish. Another packaging system from Cryovac Div., Sealed Air Corporation, used Cryovac[®] OS2000[™] polymer-based oxygen-scavenging film, which has applications in different food products such as smoked meat products and processed meats [80]. On the other hand, polymer sensors combining oxygen and carbon dioxide measurements in a single sensor [102] have been employed to smart packaging systems in many recently developed packaging systems. There are several accepted applications of polymer-based sensors : The ripeness of the pear is determined by detecting volatile aromatic compounds, or the freshness of the fish is determined by monitoring the concentration of volatile amines [103]. Nicolas et al. [81] developed a polymeric solid-state CO₂ sensor that uses phosphorescent Pt-porphyrin for food packaging applications.

The use of stimuli-responsive materials in the food packaging industry is a new strategy to get markedly improved packaging properties. However, the topic of using stimuli-responsive polymers in many food processing or packaging industries is still a challenge.

1.4.2 Agriculture

Over the past few decades, using more advanced agricultural methods (high-tech machinery, resources, and chemicals) for analyzing or monitoring soils and crops has been a research trend in agricultural planting to get more information and evaluate their maturity and health status. Among these methods, incorporation of stimuli-responsive polymers as sensors into fertilizers and pesticides to respond to the external environment is a promising field for residue analysis of soils and crops [104, 105].

The application of fertilizers and pesticides has a significantly great effect on crop productivity, and the major drawback of conventional applications, in general, is the loss depending

on the mode of application and weather conditions. Instead, the applications of these chemical products have been expected to transform into smart agrarian practices with more functional properties. As such, it is very interesting to combine fertilizers and pesticides with stimuli-sensitive polymers [106]. The products used in agriculture may get the properties sensitive to pH, light, temperature, biological environment from stimuli-responsive materials, which can be used to formulate respond to surrounding microenvironment intelligently and smartly eliciting a better and controlled release. For instance, Zhiyan et al. successfully developed glutathione-responsive carboxymethyl chitosan systems for controlled release of Diuron herbicide with the pre-emergence treatment of target species (*Echinochloa crus-galli*), and their results showed that it will be a promising candidate for controlled release of pesticides in agriculture [82]. Chi et al. [83] developed core-shell attapulgite-NH₄HCO₃-glyphosate/amino silicone oil-poly(vinyl alcohol) (PVA) nanocomposites that offered temperature-responsive controlled release of glyphosate herbicide. Another work done by Liu et al. [107] used modified soybean protein isolate and carboxymethyl cellulose by the hydrazone formation to synthesize pH-responsive avermectin nanoparticles. On the other hand, hydrogels are cross-linked networks of polymers having high water retention capacity and can be used for the application of fertilizer with responsiveness towards temperature, pH, enzymes, etc. [84]. Chen et al. [84] fabricated an environmentally responsive cellulose-based hydrogel using hydroxypropyl methylcellulose for the controlled release of water-soluble fertilizers, and this study showed that it has the potential to be used as controlled release devices in horticulture and agriculture. Another study reported an anion-responsive carbon nanosystem prepared using polyethylenimine-modified hollow/mesoporous carbon nanoparticles to improve selenium utilization efficiency in vegetables [107].

The presence of stimuli-responsive polymers in fertilizers and pesticides open more chances for many possibilities in the development of modern agriculture. However, despite many positive aspects of blending fertilizers and pesticides with responsive materials, careful evaluation

is still required before using these technologies for crops in the future.

1.4.3 *In vitro* Biomedical Diagnostics

Hoffman et al. designed a smart polymer–biomolecule conjugate for immunoassay that was based on the conjugation of an antibody to poly(*N*-isopropylacrylamide) (PNIPAAm). In order to capture an antigen such as biomarker of hepatitis or AIDS, blood test sample includes smart bioconjugate. Consecutively, second labelled antibody was added, and that detection antibody was designed to affinity link to the same antigen. In the end, to separate the phase-labelled immune complex sandwich, the solution was warmed. This assay was similar to the enzyme-linked immunosorbent assay (ELISA), except that this was performed in solution with a last step named phase separation. This method, in comparison with the typical multi-well plate ELISA , was much faster and just as accurate (Figure 1.3).

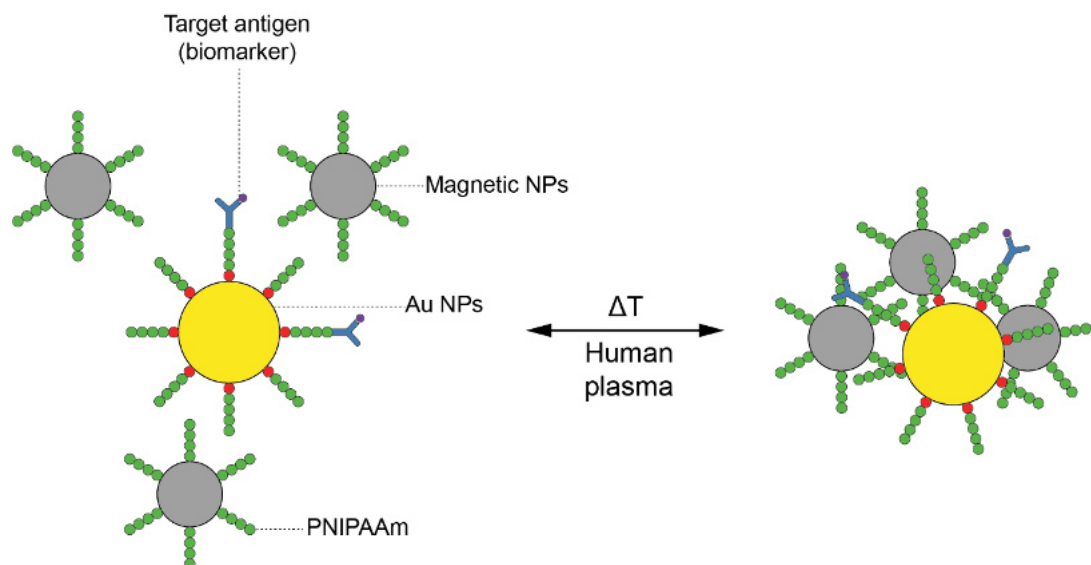


FIGURE 1.3 – When PNIPAAm is coated on magnetic nanoparticles (mNP) and gold nanoparticles (Au-NP), it acts to aggregate or ‘glue’ the NPs together when the temperature is increased above the LCST of PNIPAAm.

Stayton & Hoffman et al. have recently applied smart PNIPAAm technology to several novel surfaces and nanoparticle-based diagnostic systems, which use PNIPAAm coatings on microfluidic channels, on gold nanoparticles, and on magnetic nanoparticles. These smart

nanoscale systems are designed and developed for clinical immunoassays [85] (Figure 1.4).

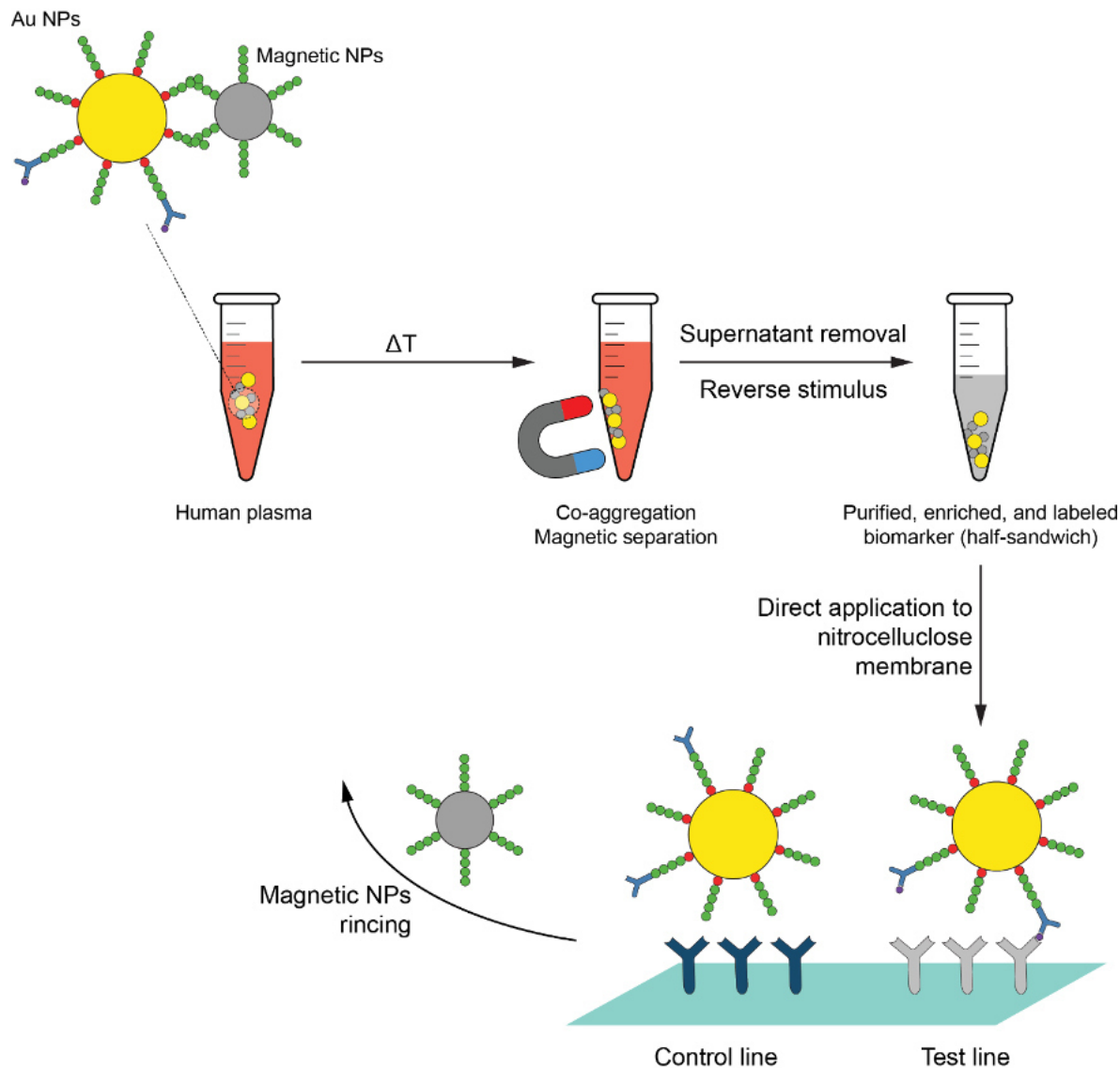


FIGURE 1.4 – Biomarkers in blood plasma test samples at RT are captured by antibodies bound to PNIPAAm-coated gold nanoparticles (NPs) that are then thermally aggregated with PNIPAAm-coated magnetic NPs and isolated and concentrated by a magnetic field. After washing the aggregates and then lowering the temperature below the LCST, the NPs are dispersed and flowed onto a lateral flow strip for biomarker assay.

1.4.4 Drug Delivery

Due to their properties and flexibility, stimuli-responsive polymers found their way into drug delivery. They were used as nanocarriers, hydrogels, micelles, and complexes that can

safely carry and protect the drug through in vivo circulation and release it in the desired site due to environment change. In addition, SRP were used in drug delivery as coating materials for drug tablets and nanocarriers [85].

Enteric coating or enteric capsule is a polymer layer added to drug tablets to increase the efficiency of the drug by protecting the tablet from early degradation [108]. Two types of enteric coatings are popular. One is based on copolymer of methacrylic monomers, and the other is based on ethylcellulose. Both types have a pH-sensitive profile. They are hydrophobic at gastric pH that restricts the release of the drug, and they become hydrophilic at intestinal pH allowing the drug to be released in the intestines, thereby protecting it from gastric degradation. This will improve the efficiency of oral drug delivery [85]. This characteristic was exploited to deliver peptides and protein through oral route. Mucoadhesive intestinal patches loaded with insulin were coated with ethylcellulose to secure a safe passage for a therapeutic dose of insulin through the digestive system to be released near intestinal mucosa.

In vivo results showed that these patches induced dose-dependent hypoglycemia in normal rats with a maximum drop in blood glucose levels of 75% [90]. In another study, pH-sensitive chitosan and poly(γ -glutamic acid) nanoparticles were loaded with insulin, freeze-dried, and coated with Eudragit[®] S100 and Eudragit[®] L100-55 capsules. After in vivo oral administration in diabetic rats, it was found that intestinal absorption of insulin was enhanced, and the relative bioavailability was about 20% [91]. Light-responsive polymer coating was also used for insulin delivery. Gold nanoparticles loaded with insulin and coated with hydrophobic ethylcellulose were developed. By applying near-infrared irradiation, gold nanoparticles are heated, which led to reversible collapse of the polymer network, resulting in the formation of porous structure, and therefore, a rapid diffusion of insulin was allowed. It was also found that by controlling the irradiation, insulin dosing in diabetic rats can be controlled [92].

Stimuli-responsive polymers were also used as coating materials in the development of core-shell organic-inorganic drug nanovehicles. Magnetite nanoparticles were coated with the temperature-responsive biopolymer poly(*N*-isopropylacrylamide-*co*-*N,N*-dimethylacrylamide) to form a core-shell structure with a size of 8 nm. Physicochemical characterization demonstrated the suitability of such system in magnetic drug delivery and in magnetic resonance imaging by combining the advantages of magnetic nanoparticles and stimuli-responsive polymers [93]. Core-shell nanocarriers were also used for the delivery of anticancer agents. Magnetic core-shell nanoparticles were synthesized using poly-*N*-isopropylacrylamide-*co*-itaconic acid containing thiol side groups as a thermo- and pH-responsive polymer. Particles were used as a vehicle for doxorubicin with a size of 50 nm and a high loading capacity (55%). The pH and temperature triggered the release of doxorubicin at tumor tissue environment, which was 39% higher than in the physiological conditions. In addition, this carrier shows no cytotoxicity while inducing an efficient anticancer effect *in vitro*, suggesting its suitability as a drug carrier in general and as an anticancer agent in specific [94].

SRP coatings are, in conclusion, a very promising agent for drug delivery, especially when it comes to oral administration of therapeutic peptides. Until now, this topic remains a challenge in pharmaceutical research.

1.4.5 Sensors

Sensors are devices that can convert an input received from a surrounding environment into an output signal that can be transformed into readable data. The ability of stimuli-responsive polymers to interact with the surrounding environment makes them a good candidate for the fabrication of sensors. Different stimuli-responsive sensors were developed, such as those responsive to temperature, pH, CO₂, and biological environment. Moreover, stimuli-responsive polymer-coated nanoparticles have gained attention in sensing research due to the optical properties of nanoparticles.

Gold nanoparticles coated with poly(*N*-isopropylacrylamide) were developed as colorimetric temperature and salt sensors. Polymer was synthesized by RAFT polymerization and grafted into nanoparticles by the ligand exchange process. It was found that with increasing temperature, these particles can change their color from red to purple to blue due to the electronic coupling of the surface plasma on resonance caused by the aggregation of gold nanoparticles. In addition, it was found that the range of temperature sensitivity increases in the presence of salt due to charge screening [86]. In another study, gold nanoparticles were used to develop CO₂ sensors. Poly(*N*-(3-amidino)-aniline), a CO₂-responsive polymer, was grafted onto the surface of the particles, and in the presence of dissolved CO₂, it can swell and detach from the surface of the particles due to the protonation of its amidine group and the formation of hydrophilic amidinium. This change can lead to the aggregation of the nanoparticles and a change in color. The limit of detection of this sensor was identified at 0.0024 hPa [87]. SRP were also used to produce highly sensitive fiber optic marine salinity sensors. Long-period gratings were coated with ionic-strength-responsive chitosan (CHI)/poly(acrylic acid) polyelectrolyte multi-layers by layer-by-layer assembly method. In the presence of NaCl, a shrinkage in the coating layer and salt ion doping occur, leading to an increase in water content and resulting in a light shifting from red to blue. The blue-shift increases with the increase in salt concentration. It was also noticed that polymer-coated systems have a higher sensitivity than the non-coated ones [88].

Biosensing was also a target for SRP. Platinum electrodes coated with a polymer-polymer complex of phenyl boronic acid with tertiary amine moieties and poly(vinyl alcohol) (PVA) were developed as glucose level sensors. The system was tested in a glucose-rich Dulbecco's phosphate-buffered saline solution at pH 7.4. It was found that in the presence of glucose, a change in the swelling of the polymer layer is induced, which leads to an increase in the diffusion of ion species and thus increases the measurable current change. This glucose sensor was

proven to be of high selectivity and suitable for measuring the physiological concentration of glucose since current changes were proportional to glucose concentration in the range 0–300 mg/dL [89]. Another glucose sensing strategy was to develop an edible electrochemical biosensor with an important resistance to extreme acidic conditions. A direct and stable glucose monitoring was achieved using edible materials such as olive oil and activated charcoal as carbon paste biosensors. These materials were able to protect the embedded glucose oxidase enzyme from strong acidic conditions. Moreover, the electrode was coated with pH-responsive enteric coatings (Eudragit[®] L100 and Eudragit[®] EPO), which allow the control of the activation at different values of pH corresponding to gastric and intestinal conditions [109].

The presence of a high range of biocompatible SRP opens up the opportunity for many possibilities in the development of biosensors. However, an improvement in selectivity, stability, sensitivity, and output readability is always required [110].

1.4.6 Cosmetics

In general, polymers are the second-largest category of ingredients in the composition of cosmetics and personal care products. Stimuli-responsive polymers are interesting in cosmetics because they help the formulation of cosmetics to exhibit desired characteristics in the storage container. Upon the heating (above the threshold temperature), the thermally reversible viscosifying polymers show a dramatic increase in the solution viscosity. In the aqueous compositions consisting of polymers possessing a poly(2-acrylamido-2-methylpropanesulphonic acid) backbone and grafted chains of polyoxyethylene and polyoxypropylene or polyoxybutylene, thermal gelling was observed.

It is possible to use gelation in response to the stimuli such as temperature as a processing aid, for instance, in the case of multiple emulsions preparation. To obtain water/oil/water multiple emulsions normally, it is needed, for the first time, to prepare the internal emulsion

in a separate way from the external base and afterwards to mix slightly the phases together to prevent the internal water phase from escaping into the external aqueous phase. Processing complications are raised when the viscosity of the oil phase is considerably higher than that of either of the aqueous phases. According to a research performed by Mercier, usage of amphipathic reverse thermal gelling polymers can increase the viscosity of both the internal and external aqueous phase, allowing a one pot mixing of multiple phase emulsions without breaking the W/O while avoiding the mixing of the internal aqueous phase and the external aqueous phase [95].

1.4.7 Textiles

In order to bring an added value to functional textiles, coating and lamination can be the interesting strategies. Due to the wider applications of the functional textiles, the use of these techniques is boosting since coating and lamination extend the range of smart performance properties of textiles. To design fabrics with functional properties, coating and lamination techniques are employed. Furthermore, thanks to the widespread application of coating and lamination over the range of technical textiles sectors, improve functionality and durability. Coating and lamination are including : WVP, waterproofness, increased abrasion, flame, and UV resistance or phase change materials. Usually, coatings (often in liquid form) are applied to fabrics during the preparation stage. The preparation of laminate membrane is needed to be applied on the textile consecutively. Coated and laminated textiles widespread application across the different types of technical textile sectors are including antibacterial coatings, waterproof breathable, water vapor and air permeable, UV resistance, phase change materials, etc. [1, 111]. The way in which the coatings and lamination stick to the fabric surface determines the method of their communication with the fabric. Since coating is applied in liquid form on the fabric, it covers the surface of the fabric and penetrates the fabric structure, filling the air pockets and bridging the interstices. Occasionally, the end product is defined as a composite that is attributed to the combination of textile and non-textile. The tear strength and

thermomechanical properties determine the mechanical properties of the fabric [96, 112, 113].

The textile institutes describe a coated textile as a material composed of two or more layers, at least one of which is a textile fabric and at least one of which is a substantially continuous polymeric layer. This polymeric layer is administered in liquid form with a solvent or water base that evaporates leaving the polymer behind and is applied to one or both the sides. Laminated textiles are formed from one or more layers of textile and non-textile components. Based on the Textile Institute, laminated or combined fabric is a material composed of two or more layers, at least one of which is a textile fabric, bonded closely together by means of an added adhesive, or by the adhesive properties of one or more of the component layers. Smart clothing is employed to keep the users warm by default, for example, in winter and then to help the body spontaneously cool down when the wearer sweats [114].

1.5 Conclusion

Stimuli-responsive polymers that can be of either natural or synthetic origin react to changes or stimuli such as pH, temperature, and light. Indeed, stimuli are divided into three main categories : physical stimuli, chemical stimuli, and biological stimuli. Thanks to this characteristic, stimuli-responsive polymers offer a vast range of functionalities in food, agriculture, drug delivery, biomedical diagnostics, sensors, textiles, and cosmetics and continue to show a great promise. The stimuli-responsive materials are divided into four classes : stimuli-responsive polymers, stimuli-responsive nanogels, stimuli-responsive structured particles, and stimuli-responsive membranes. The presence of a wide range of polymers with a responsive ability to external stimuli, opens the possibility to a vast array of applications. While natural polymers were used in food, agriculture, and drug delivery for human administration, packaging, and microbial and oxidation protection, synthetic polymers are also used as sensors, scavenging agents, and many more. Finally, despite the vast knowledge we already have in

the topic, more promising findings are being uncovered on yearly basis that can open the doors to a larger niche of applications.

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Chapitre 2

LES POLYMERES pH-SENSIBLES : ETAT DE L'ART ET APPLICATIONS

Étude bibliographique acceptée pour publication sous la
forme d'une review dans *Polymers for Advanced
Technologies*, doi :10.1002/pat.5230 .

Cette deuxième revue bibliographique se situe dans la continuité de la première et aborde plus spécifiquement les polymères pH-sensibles [1]. Ces polymères sont connus pour leur sensibilité au pH de leur environnement. Leur réponse aux modifications du pH environnant peut se traduire par des modifications de leurs propriétés telles que leur conformation ou leur solubilité [2]. Mis à part leur étude dans l'industrie pharmaceutique et le domaine biomédical où ils sont employés dans la délivrance ciblée en fonction du pH de principes actifs médicamenteux [3, 4, 5, 6], ces polymères trouvent application aujourd'hui dans d'autres domaines divers et variés. Ils sont en effet étudiés pour leurs potentialités dans des dispositifs de capteurs/actionneurs [7], dans la fonctionnalisation de surfaces et de membranes [8, 9, 10], dans le développement de dispositifs de séparation [11] ou encore comme stabilisants dans la synthèse de nanoparticules catalytiques [12], etc.

La revue bibliographique qui va suivre est divisée tout comme la première en trois grandes parties. Dans la première partie, nous introduisons la notion de polymère pH-sensible et abordons de façon succincte les propriétés de ces polymères. De plus, une classification des polymères pH-sensibles est proposée. Cette classification est basée dans un premier temps sur l'origine des polymères. Ceci nous a emmené à distinguer d'une part les polymères pH-sensibles d'origine naturelle essentiellement dérivés de polysaccharides et d'autre part les polymères pH-sensibles synthétiques. La catégorie des polymères pH-sensibles synthétiques nous a conduit à présenter les diverses techniques employées pour leur élaboration. Dans un second temps, une classification basée sur la structure des polymères est proposée. La deuxième partie de cette revue est consacrée aux polymères sensibles à plusieurs stimuli incluant une réponse au pH. Ces polymères sont fréquemment rencontrés dans la littérature et occupent une place importante parmi les polymères stimulables. En effet, en termes d'applications, ces polymères présentent l'avantage de s'adapter et de mimer au mieux les environnements complexes que peut présenter le corps humain par exemple où la libération de principes actifs peut être catalysée à la fois par le pH, la température et le potentiel redox

du milieu environnant [13, 14, 15]. Nous abordons donc dans cette seconde partie quelques exemples de polymères sensibles à 2, 3 voire 4 stimuli différents. Dans la troisième et dernière partie, une place importante est consacrée aux applications des polymères sensibles au pH avec des exemples concrets. Nous abordons dans cette partie entre autres les copolymères d'acide méthacrylique, d'esters d'acide méthacrylique, de méthacrylate de diméthylaminoethyl connus sous leur nom commercial d'Eudragit et notamment leur utilisation comme vecteurs thérapeutiques y compris les types E100 et L100 qui vont faire l'objet de notre partie expérimentale. L'Eudragit E100 trouve principalement application comme matériau d'enrobage dans le masquage de l'amertume ou de l'odeur de certaines molécules actives destinées à une administration par voie orale et dans leur protection contre la lumière et les moisissures. L'Eudragit L100 quant à lui est utilisé principalement dans l'enrobage et dans l'encapsulation de molécules actives en vue de leur protection contre l'acidité et les sucs gastriques et de leur libération au niveau de l'intestin où le copolymère s'y trouve sous forme expansée ou soluble [16, 17]. Il joue un rôle important dans l'augmentation de la biodisponibilité de nombreux principes actifs médicamenteux [18, 19]. Quelques remarques sur les perspectives dans le développement et l'utilisation des polymères sensibles au pH sont introduites. Nous introduisons notamment leur utilisation grandissante dans le développement d'emballages alimentaires intelligents [20, 21]. Cette revue présente ainsi une mise à jour de l'état de l'art sur les polymères sensibles au pH et leurs applications.

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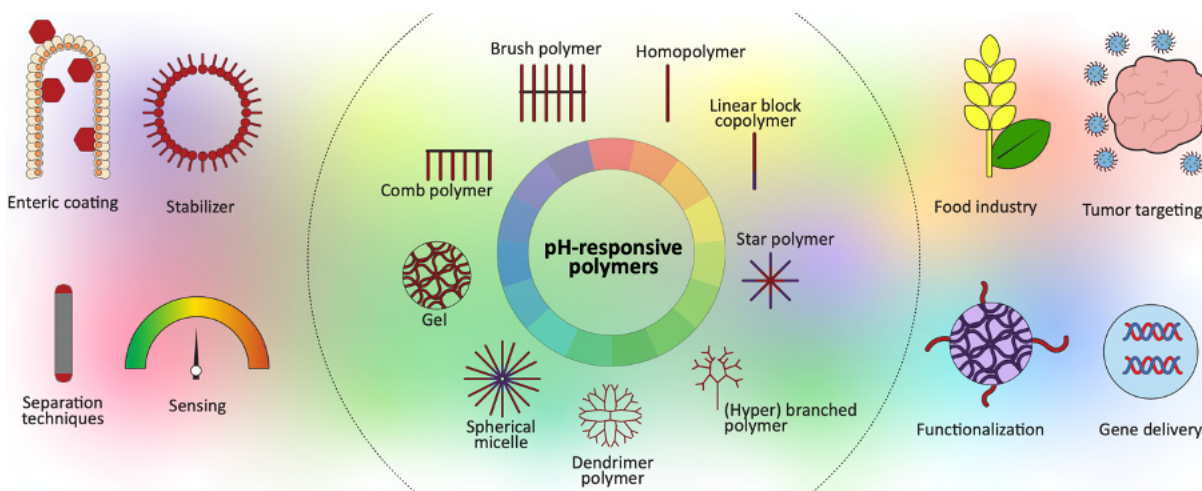
pH-SENSITIVE POLYMERS : CLASSIFICATION AND SOME FINE POTENTIAL APPLICATIONS

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Abstract :



Stimuli-responsive materials in general and pH-responsive polymers especially have gained rising interest during the last two decades. Their unique properties that arise from their ability to exhibit sharp and reversible changes in response to environmental pH conditions have made them suitable for various applications such as drug delivery and specific body sites targeting, sensing and actuation, membranes functionalization, separation techniques, agriculture and food industry or even in chemical industries. In the present review, the focus was set on the general characteristics of pH-responsive polymers in terms of origin, chemical composition and preparation. Moreover, some of the important and recent applications are reported and discussed.

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Keywords : pH-responsive polymers, smart polymers, drug delivery, sensing and actuation, separation methods, surface functionalization.

2.1 Introduction

Polymer-based particles are widely used for diverse applications, especially for the encapsulation of drug molecules, mainly because of their good biocompatibility and bio-elimination [1]. As drug carriers, they are able to efficiently deliver therapeutic agents to target sites. This is due to the polymeric properties which allow the preparation of particles with controlled size, size distribution, permeation, flexibility and solubility [2, 3].

Surface properties of polymers are improved chemically, physically or biologically in order to increase their biocompatibility [1]. The biodegradability of polymers/polyelectrolytes is controlled by incorporating a variety of labile or hydrolysable groups such as ester, carbonate, amide, urea or urethane in their backbone [4]. Thus, research has led to the development of a new class of polymers, which are stimuli-responsive. These polymers are materials that are sensitive to physico-chemical changes in their surrounding environment. They are capable of detecting small environmental variations and react with self-assembly or dramatic changes in their physico-chemical properties. These polymers undergo structural and conformational changes as a response to the variation of environmental conditions, such as pH, temperature, solvent, salt ionic strength, light, magnetic or electrical fields. One of their fundamental characteristics remains the reversibility of the modifications i.e. their ability to return to their initial state as soon as the stimuli responsible for the physicochemical properties' modification is removed (exception made for structured linked degradable systems). Stimuli-responsive polymers can be made only of natural or synthetic polymers or by incorporating a responsive compound or function along an existing polymer's backbone. Interest in these materials has been fastly growing since the two last decades because of a multitude of emerging applications.

Environmental changes or stimuli are of three orders : physical stimuli (mechanical stress, electrical/magnetic field, ultrasounds, light, temperature), chemical stimuli (electrochemical, pH, ionic strength) and biological stimuli (enzyme, biomolecules) [5, 6, 7]. Figure 2.1 shows the different classes of stimuli with the type of modifications induced by each category.

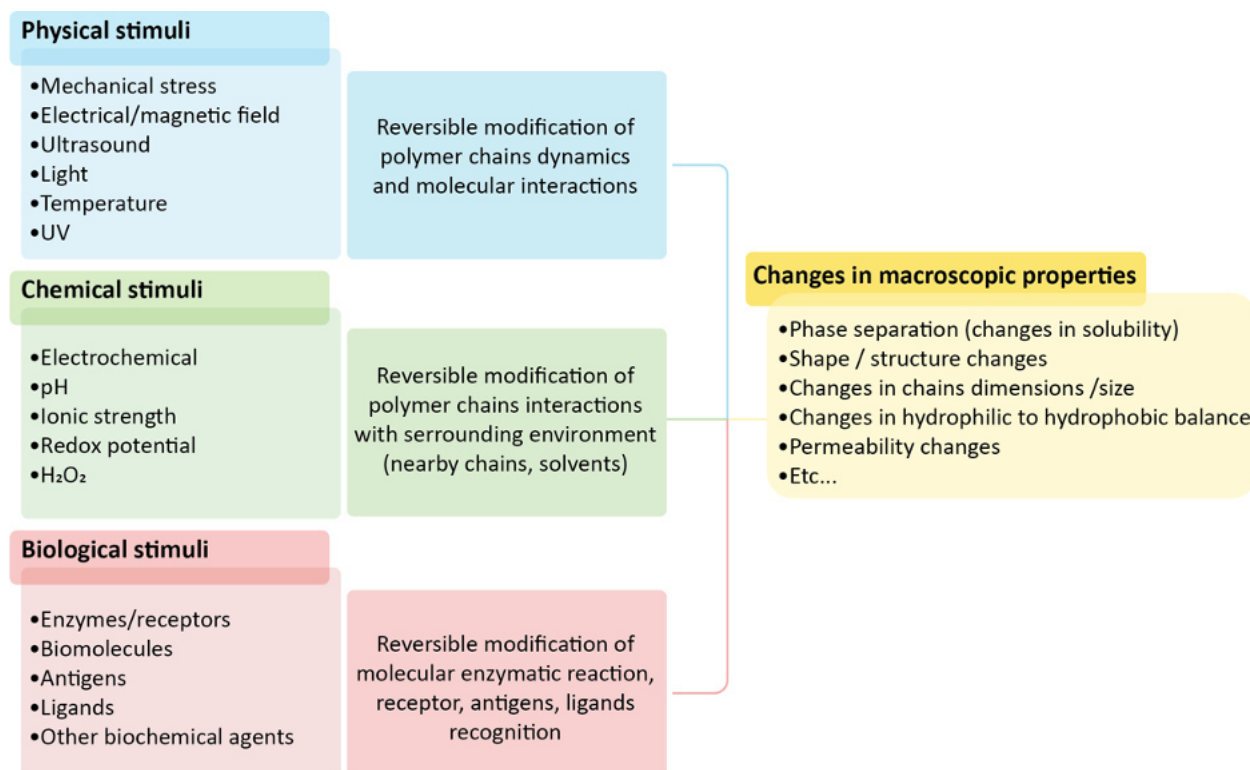


FIGURE 2.1 – Classification of stimuli-responsive polymers with their induced modification.

Physical stimuli such as temperature, light, electric or magnetic fields cause intermolecular interactions. On the other hand, chemical stimuli affect the molecular structure of the polymer by the addition of chemical agents [8]. With these stimuli, one may find pH-responsive, solvent-responsive, ionic strength-responsive, chemical agent-responsive or biologically responsive polymers.

pH-sensitive polymers (PRPs) respond to environment pH variation throughout structural and property changes such as surface activity, chain structure, conformation, solubility

and configuration. pH-sensitive polymers contain acidic or basic groups that can either accept or donate protons in response to the fluctuation of the environmental pH. Different PRPs categories exist and according to the classification criteria, weak base can be distinguished from weak acid, biopolymers, degradable polymers from synthetic ones. They find application in drug delivery, gene delivery, actuation and sensing/biosensing, separation techniques etc. [9].

This review deals exclusively with pH-sensitive polymers. Their important properties, classification and structure are firstly introduced. Multiple-responsive polymers with pH-responsiveness are highlighted in the second part of this review. A special focus is dedicated to the different and recent applications of pH-responsive polymers.

2.2 Characteristics of pH-responsive polymers

PRPs behave with respect to the surrounding pH by undergoing structural and property changes such as surface activity, chain conformation and solubility. The nature of the changes depends on the pH-responsive material structure [10]. Considering a homopolymer, pH variation gives rise to flocculation, chain collapse-extension, or precipitation. For pH-responsive block copolymers or reticulated structured PRPs, the response to pH modification is made through self-assembly such as formation of micelles, unimers, gels, vesicles, swelling/deswelling, etc. [11]. Recall that PRPs are materials that include in their structure weak acidic or basic groups that either accept or release protons in response to a fluctuation of the environmental pH. Polyanions or polyacids have ionizable pendant acid groups, such as carboxylic acid (COOH), sulfonic acid (SO₃H), or phosphonic acid (PO₃H₂), along the polymer backbone whereas polycations or polybases contain basic groups such as amines (NH₂) either in their structural backbone or as a pendant group. Ionization of these functional groups with respect to the surrounding pH results in a modification of the polyelectrolyte

structure [11, 12].

Figure 2.2 presents a schematic representation of a polyacid and a polybase state depending on the ionization degree of the ionic chain group. A polyacid exhibits an expanded state when medium $\text{pH} > \text{pKa}$ whereas the polymeric chains collapse at pH values $< \text{pKa}$. However, for a polybase, above the value of pKb ($\text{pH} > \text{pKb}$), polymer chains collapse, inversely they expand at $\text{pH} < \text{pKb}$.

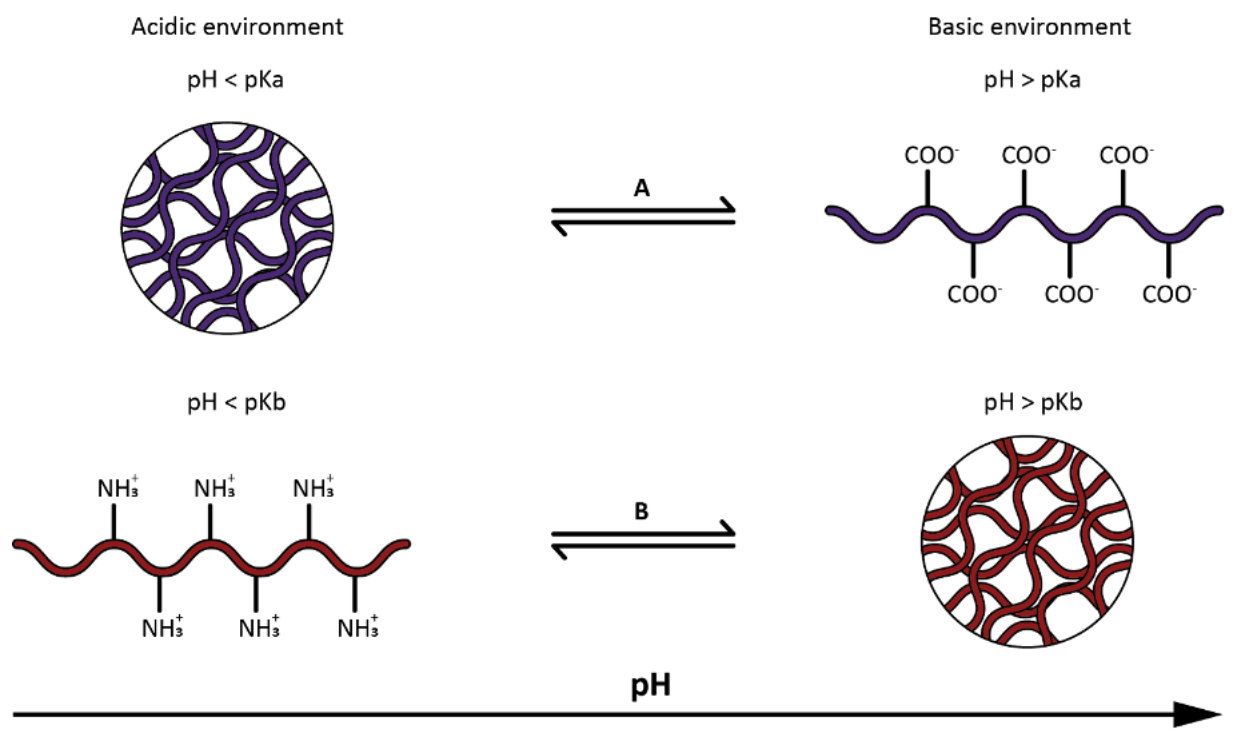


FIGURE 2.2 – (a) Polyacids and (b) Polybases polymeric chains state depending on the ionization degree.

One of the well-known and largely described behaviors of these materials is the swelling/deswelling of the polymers depending on the state of their ionizable groups. Typically, these polymers are water-soluble when charged and become water-insoluble when neutral. The phenomenon is that when the ionizable groups become neutral, electrostatic repulsion forces disappear within the polymer network, and hydrophobic interactions dominate.

The charge status in these materials is readily reversed by returning to the starting pH of the solution ; the switching behavior of the PRPs is also reversible [13].

In practice, for a specific application, one should choose the pH-responsive polymer or material according to its pKa value and the expected pH responsiveness range. pH-responsive materials preparation techniques allow the customization of polymeric materials in order to have a certain pKa value and to achieve a specific task. Transition pH dictated to the pH-responsive material by its pKa (for acidic material) and pKb (for basic material) can thus be tuned by modifications that affect hydrophobic or electrostatic interactions [14, 15]. Methods employed to tune pKa are hydrophobic modification (incorporating different hydrophobic groups or changing the length of hydrophobic chains lead to pKa shift), copolymerization of PRPs with non-ionizable or ionizable polymers (additional polyelectrolytes that change both hydrophobic interactions and electrostatic repulsion lead to pKa shift), and acid-labile linkages as well [16].

2.3 Natural pH-Responsive Polymers

Considering their origin, natural PRPs are distinguishable from synthetic ones. A pH-responsive conformation with solubility changes is a common behavior in biopolymers [17]. The use of natural polymers prevails because of their abundance in nature, biodegradability, non-toxic behavior and biocompatibility, and ability to be modified [18].

Hyaluronic acid, alginic acid, heparin, chitosan and the cellulose derivatives (carboxymethyl cellulose, carboxymethyl dextran) are examples of natural PRPs.

2.3.1 Alginate

Alginate, one of the most abundant polysaccharides, is extracted from brown seaweed, and used extensively in food, pharmaceuticals, and regenerative medicine [19, 20]. Alginate consists of a block copolymer of β -D-mannuronic (M) and α -L-guluronic acid (G) in varying sequential arrangements and proportions [21] (Figure 2.3). It is an acidic polysaccharide bearing carboxylic groups, whose pKa is at 3–4 [22]. Both mannuronic and guluronic acid residues have carboxylic functional groups in their structure which are at the origin of pH-sensitivity of alginate [23]. The high acid content allows alginic acid to undergo spontaneous and mild gelling in the presence of divalent cations, such as Ca^{2+} , Ba^{2+} , Sr^{2+} , and Zn^{2+} , the formed gel shows variable swelling profile in response to pH variation [24]. These mild gelling properties are pH-dependent and allow the encapsulation of various molecules or even cells within alginate gels with minimal negative impact [25]. Moreover, at low pH prevailing in the gastric environment, alginate shrinks and retains encapsulated molecules [13]. The length of the M- and G-blocks and their sequential distribution along the polymer chain vary depending on the source of alginate.

2.3.2 Hyaluronic acid

Hyaluronic acid (HA) or hyaluronan is a naturally occurring linear polysaccharide composed of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide (Figure 2.3). At neutral pH, HA acts as an anionic polyelectrolyte since the pKa of the carboxylic acid groups is approximately 3–4, which makes HA highly hydrophilic. Due to its ability to absorb water, it expands up to 1000 times its solid volume, leading to a loose, and hydrated network [26]. The high content of hydroxyl and carboxylic acid groups provides added functionalities via conjugation, chemical bonding, and cross-linking [27] promoting the preparation of pH-sensitive hydrogels [28, 29, 30]. pH-sensitive HA nanoparticles were prepared by L. Han et al. [31] as oral delivery carriers with the advantage of protecting the loaded insulin against the stomach's strong acidic environment. Miyazaki et al. [32] reported the synthesis of hyaluronic

acid (HA)-based pH-sensitive polymers designed as multifunctional polymers having not only pH-sensitivity but also targeting properties to cells expressing CD44, which is known as a cancer cell surface marker.

2.3.3 Carboxymethylcellulose

Carboxymethylcellulose is a typical anionic cellulose derivative in which carboxymethyl groups are bonded to hydroxyl groups of the glucopyranose monomer (Figure 2.3). The carboxymethyl groups of this polysaccharide are ionizable above their $pK_a=4.3$ [33]. On this basis, E. Akar et al. [34] prepared and characterized a pH-sensitive sodium carboxymethyl cellulose-based hydrogel by using fumaric acid (FA) as a crosslinking agent. Chemically modified carboxymethyl cellulose-based hydrogels with pH-responsive properties have been reported in literature for the controlled release of molecules such as Rhodamine B dye [35], isoliquiritigenin in inhibiting growth of acne through transdermal delivery [28], or lysosomes [36]. In general, smart cellulose-based hydrogels have wide applications in the fields of agriculture, food, tissue engineering, and drug delivery [37].

2.3.4 Chitosan

Chitosan (Ch) is a naturally occurring polysaccharide with randomly distributed *N*-acetyl glucosamine (2- acetamido-2-deoxy- β -D-glucopyranose) and glucosamine (2- amino-2- deoxy- β - glucopyranose) units (Figure 2.3). This copolymer is obtained by alkaline deacetylation of chitin.

The main commercial sources of chitin are crustacean shell wastes. Because of the physicochemical and biological properties of chitosan, especially its biocompatibility, biodegradability, non-toxicity, capacity of metal ion adsorption, excellent film forming capability, etc., it found application in medical and pharmaceutical fields, food industry, agriculture, wastewater treatment and other areas [38].

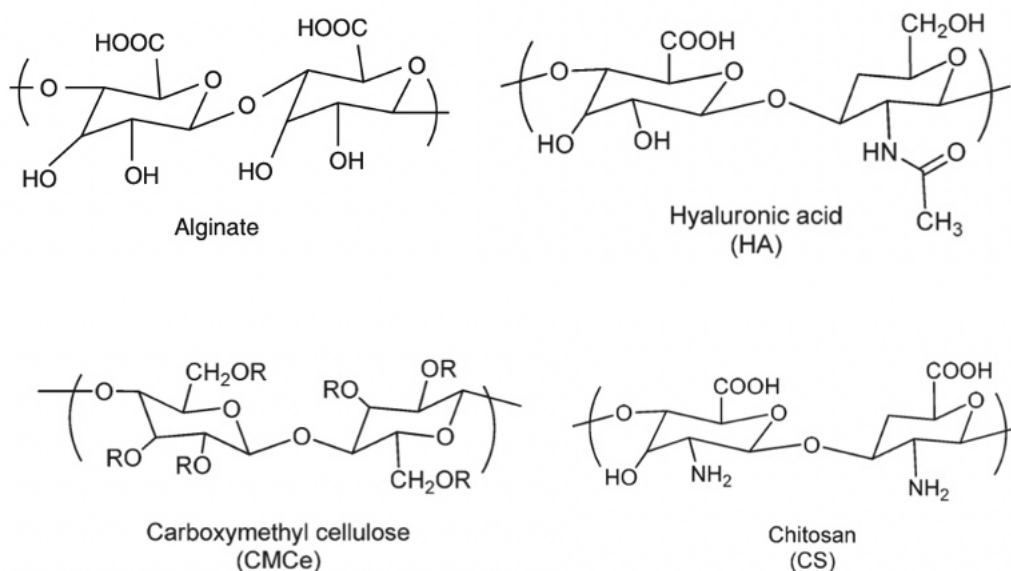


FIGURE 2.3 – Chemical structure of commonly used natural pH-responsive polymers [11]. With Copyright permission

Chitosan exhibits a pH-sensitive behavior as a weak polybase due to the large quantity of amino groups on its chain. Chitosan dissolves easily at low pH while it remains insoluble at higher pH ranges. The mechanism of pH-sensitive swelling involves the protonation of its amine groups under low pH conditions. The protonation leads to chain repulsion, diffusion of proton and counter ions together with water inside the gel and dissociation of secondary interactions [39]. This pH-sensitivity has been reported for drug delivery applications [40, 41, 42]. Recently, S. Gaware et al. [43] reported the synthesis of curcumin loaded pH-sensitive nanocomposites made of chitosan and silica. They showed a pH-dependent release of the curcumin. They concluded on the tunable release profile of the active molecule using the release media pH. pH-dependent drug release using chitosan-based polymeric materials was also shown by other authors [44, 45]. As an innovative application, P. Ezati et al. [46] synthesized chitosan-based pH-dependent color-changing film. They incorporated alizarin for active and smart food packaging applications. The composite film showed a vivid color change from slightly yellow to purple in response to a pH variation in the range of 4–10. The chitosan/alizarin

film showed antibacterial, antioxidant, and pH-responsive color-changing properties.

2.4 Synthetic pH-Responsive Polymers

Although the use of natural polymers is of common interest because of their abundance, degradability, biocompatibility and ability to be modified, synthetic PRPs exist and are used for diverse applications. Among these specific synthetic polymers, derivatives of polypeptides such as poly(L-glutamic acid) (PGA), poly(histidine) (PHIS), and poly(aspartic acid) (PASA) are biocompatible and degradable pH-sensitive polymers [11]. Controlled/living radical polymerization techniques were developed and used to prepare well-defined homopolymers or block copolymers under simple and less stringent reaction conditions than anionic polymerization and group transfer polymerization (GTP). These controlled/living radical polymerization methods include atom transfer radical polymerization (ATRP), reversible addition fragmentation chain transfer polymerization (RAFT) and nitroxide-mediated polymerization (NMP), which is one type of stable free-radical polymerization (SFRP). ATRP and NMP control chain growth by a reversible termination-process step, while RAFT polymerization controls chain growth through reversible chain transfer [47, 48]. ATRP and RAFT allow a precise control over molecular weights and molecular weight distributions, affording polymers with well-defined topology structure [16]. In recent years, ARTP became the most popular controlled radical polymerization method used in the synthesis of PRPs due to the relative easy production process with various architectures such as block, star, gradient, brushes, and branched (co)polymers [11].

Synthetic pH-sensitive polymers will be the topic of the next section where basic pH-sensitive polymers will be listed. A classification according to their functional groups and their chemical structure will be presented.

2.4.1 Composition-based classification

Considering the nature and the localization of the pH-responsiveness group, pH-sensitive polymers may be categorized firstly into 2 groups : polymers with ionizable pendants and polymers that contain acid/base-labile linkages [11]. PRPs with ionizable pendants are cationic or anionic. The degree of ionization in a polymer bearing weakly ionizable groups is dramatically altered at a specific pH known as pKa. When the pH of the medium is modified, polymer functional groups are capable of accepting or donating protons (H^+), changing the ionization degree and the net charge on the polymer chains. This leads to the alteration of their hydrodynamic volume and conformation. As the net charge on the chains increases, the electrostatic repulsion of the generated charges causes the transition of the chains from collapsed to expanded state [17, 49]. Conversely, a decrease in the chain's net charge provokes their transition from expanded to collapsed configuration. Furthermore, altering the electrostatic charge affects the water solubility of the polymer. Increased net charge increases the hydrophilicity of the chains, leading to enhanced polymer solubility [33].

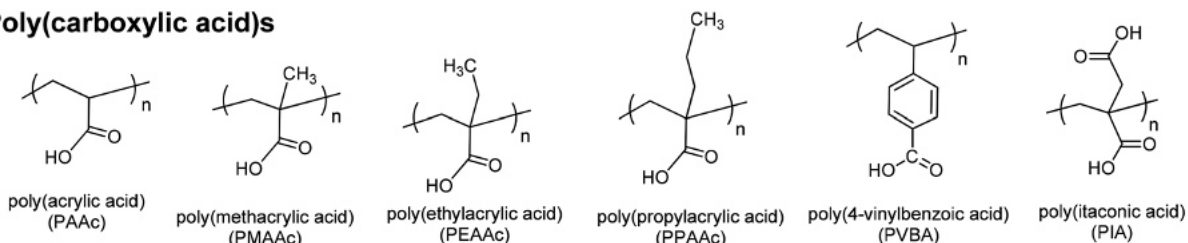
Polyacids as pH-responsive polymers

Polyacids exhibiting pH-responsive behavior contain acidic pendant groups or residues such as carboxylic acids, sulfonic acids, phosphoric acids and boronic acids. pH-responsive polyanions accept protons (H^+) in medium at low pH and release protons (H^+) at neutral and high pH throughout their functional groups. As reported by Bazban-Shotorbani et al. [33] taking example of poly (acrylic acid) which pKa value is 4.28 with acidic carboxylic pendant groups (-COOH), it is anionically charged at $pH > 4.28$ and becomes predominantly uncharged at pH below the pKa. The pKa values of polyacids, which determine the transition point of PRPs, differ from monoacids pKa and depend on their polymeric composition and molecular weight as well [50].

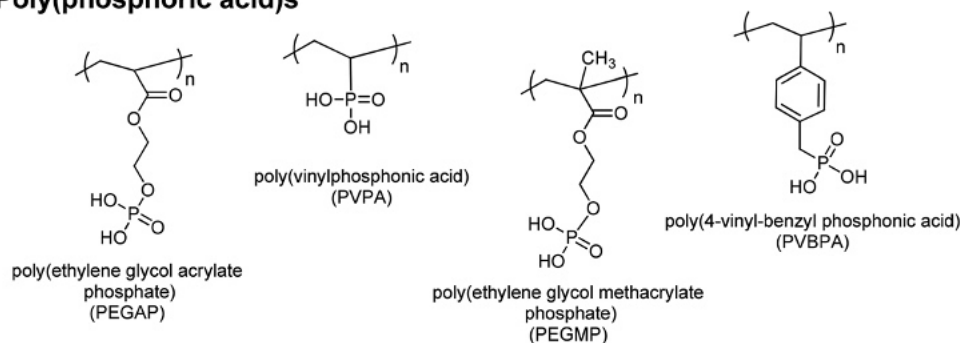
Figure 2.4 summarizes the most common acid PRPs classified according to the nature of

their functional groups.

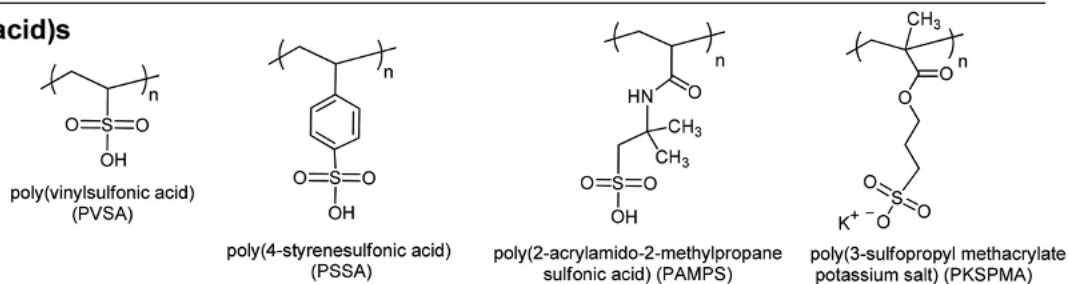
Poly(carboxylic acid)s



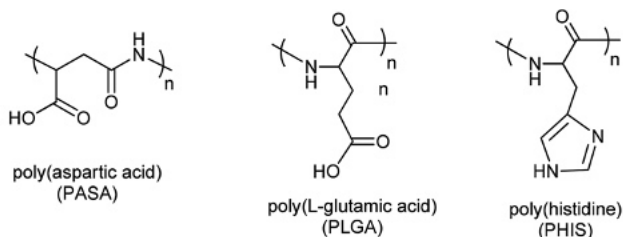
Poly(phosphoric acid)s



Poly(sulfonic acid)s



Poly(amino acid)s



Poly(boronic acid)s

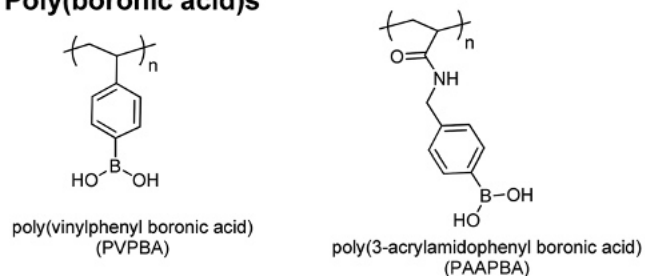


FIGURE 2.4 – Chemical structure of polyanions pH-responsive polymers classified according to the nature of their functional pendant groups [11]. With Copyright permission

Polybases as pH-responsive polymers

Basic polycations exhibiting pH-responsiveness contain basic moieties such as tertiary amine groups ; morpholino, pyrrolidine, piperazine groups ; pyridine and imidazole groups or made of dendrimers as shown in Figure 2.5 which summarizes the common polymers with their chemical structure. These polymers are protonated at high pH values and positively ionized at neutral and low pH.

Polymers with acid/base-labile linkages

Polymers with acid/base-labile linkages in their backbone are able to respond to environmental pH modifications. Their response to pH variations is made throughout the cleavage of the linkage and its degradation [16]. For instance, a pH decrease is able to trigger the reversible cleavage of acid-labile covalent bonds (such as Hydrazone), causing a hydrolysis/degradation of polymer chains or a dissociation of polymer aggregates [51]. Polymers with acid-labile linkages are most frequently used due to the fact that they are recommended in drug delivery for the design of anticancer drug carriers for tumor targeting.

Most commonly acid-labile linkages used for this purpose are Hydrazone, Acetal, Ketal, Boronate ester [16, 52]. The linkages structure, degradation mechanism and by-products after cleavage are presented in Figure 2.6.

2.4.2 Structure-based classification

PRPs present different architectures. They exhibit linear (homopolymers, di, ter, multi-block copolymers and organic/inorganic hybrid polymers), non-linear branched (branched or hyperbranched polymers) or network structures.

Different architectures found in literature are shown in Figure 2.7. The most common pH-responsive polymer structures are linear homopolymers, amphiphilic, and double hydro-

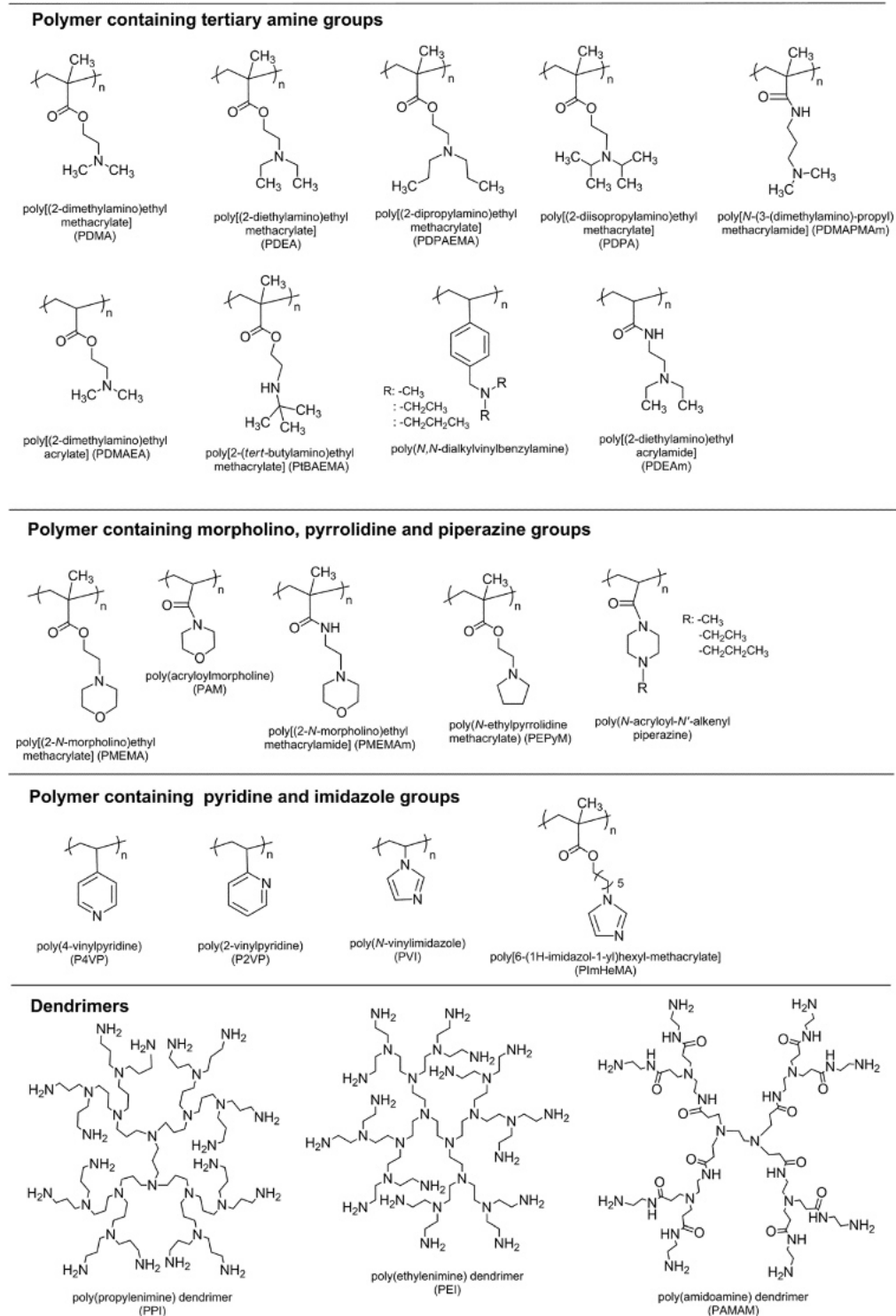


FIGURE 2.5 – Chemical structure of polycations pH-responsive polymers classified according to the nature of their functional pendant groups [11]. With Copyright permission

Bond	Structure	Cleavage conditions	Cleavage products
Hydrazone		pH~5.5 100% degradation within 200 min 10 times faster than pH 7.5	
Imine		pH~5, cleavage within 3h	
Cis-aconityl		pH~4	
Acetal		Bisacrylamide acetal with ap-methoxy substituent pH~5, half-life 5.5 min slightly acidic pH complete hydrolysis <1h	
Ketal		pH~5.5, half-life 2 h	
Orthoester		pH~5-6, 1h	
Oximes		pH~5	
Boronate ester		pH~5, cleavage in 120 min	

FIGURE 2.6 – Summary of commonly used acid-labile linkage. Adapted from [27, 16, 53, 54, 55, 56].

philic block copolymers which form micelles or vesicles, star, branched, and hyperbranched polymers, polymer brushes, dendrimers, nanogels, micro-gels, and hydrogels (macrogels) [11].

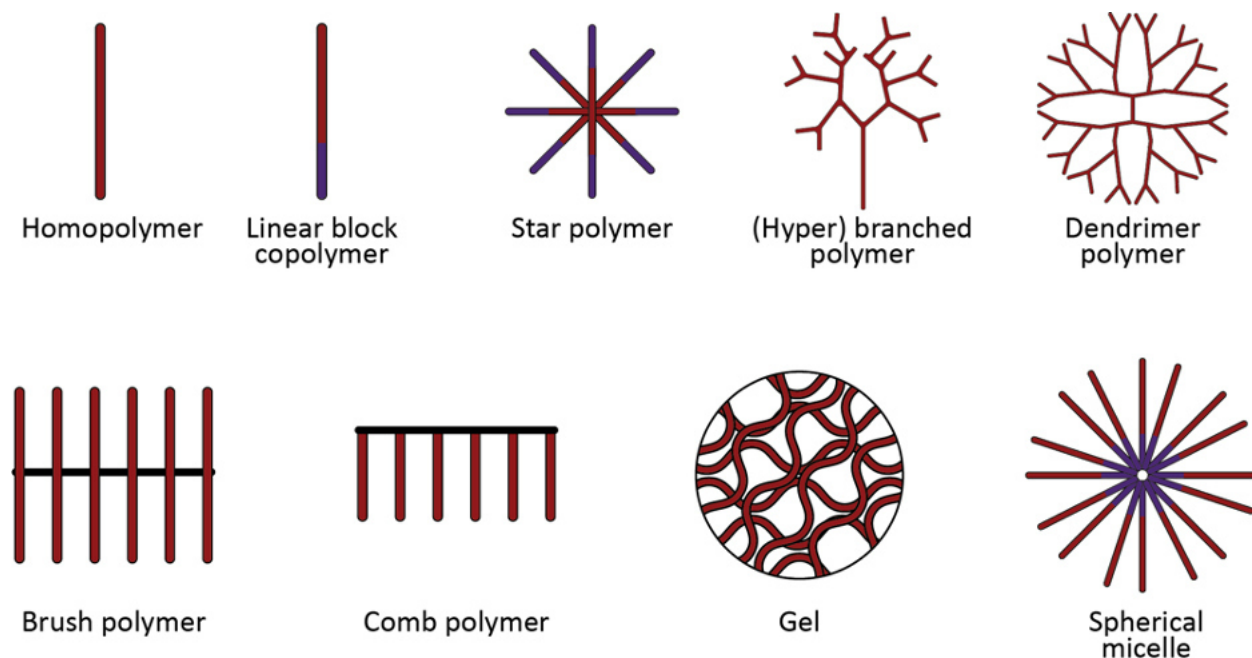


FIGURE 2.7 – Different architectures of pH-responsive polymers.

pH-responsive linear block copolymers

pH-responsive linear polymers are homopolymers, random copolymers, amphiphilic and double hydrophilic block copolymers. Regarding block copolymers, they are made of two, three or more segments. Depending on the solubility conditions, these block copolymers may experience self-assembly. Furthermore, the size of the relative blocks defines whether it will be a micelle, vesicle or a combination [57, 58, 27]. Micelle configuration is a particular property originated from the association of soluble and insoluble segments of the polymer in certain conditions which is desired and exploited in the pharmaceutical field for the delivery of active ingredients. In solution, amphiphilic block copolymers may self-assemble into micellar structures, such as spheres, which are used as nanoreactors and stimuli-responsive materials. pH-responsive amphiphilic block copolymers contain a number of ionizable groups in their

main chains and pendants; therefore, their domains can be tuned to respond to aqueous environment property changes. When the pH value is modified, these groups accept or donate protons in aqueous solution to yield polyelectrolytes, weak polyacid or weak polybase, depending on their structures and the pH values [13, 59]. Self-assembly micelle morphology is affected by parameters such as temperature, pH, salt and polymer concentrations, solvent type, and the structure/length of blocks [60]. Thus, different self-assembly structures appear according to the environmental conditions. Amphiphilic and double hydrophilic block copolymer micelles exhibit spherical, flower, worm-like, and vesicle (hollow) arrangements with pH variations [11].

pH-responsive star polymers

Star polymers contain several linear chains connected to one central core. pH-responsive star polymers bearing block/arms undergo sharp phase transitions upon responding to pH changes and form self-assembled micellar structures or undergo a change of the micelle morphology [11]. Further, branched polymers including dendritic, highly and hyper-branched and multibranch structures can also be included in the pH-responsive star polymers section. This category of PRPs with promising applications such as drug delivery and advanced coatings [61] differs from the linear analogues of identical molar mass by their compact structure (smaller hydrodynamic volume and radius of gyration) and high concentration of functional terminal groups. This confers them a higher solubility in common solvents, lower solution and melt viscosities, and modified thermal properties [62, 63].

pH-responsive brush and comb copolymers

pH-responsive brushes and combs refer to materials composed of polymeric chains (hairy-like chains) grafted to a surface or interface [64]. Polymer brushes are typically anchored to the substrate surface by physisorption or covalent chemical attachment. These materials exhibit a change in their conformation, surface energy or change state, triggered by pH modifications

[65].

pH-responsive hydrogels

Hydrogels are characterized by hydrophilic polymers that are crosslinked into an insoluble, but highly hydrophilic structure [66]. They are defined as hydrophilic polymer networks and may absorb from 10–20% up to thousands of times their dry weight in water. Hydrogels are called ‘permanent’ or ‘chemical’ gels when they are covalently crosslinked [67]. Hydrogels respond to external stimuli including surrounding pH conditions [68]. pH-sensitive hydrogels contain acidic/basic ionizable pendant pH-sensitive groups or acid/base labile linkage. Chains bearing acidic groups deprotonate at high pH, whereas the basic groups protonate at low pH [69] leading to pH-induced swelling/deswelling. The generation of electrostatic repulsive forces from ionization and charge appearance on polymer chains results in the pH-dependent swelling and deswelling process as water is either absorbed or expelled from the hydrogel network [70]. Anionic hydrogel networks contain pendant groups that are ionized in solutions at a pH greater than their acid dissociation constant, pKa. Therefore, the hydrogel swells at $\text{pH} > \text{pKa}$ because of the large osmotic pressure generated by the presence of ions. Conversely, cationic pendant groups are ionized at a pH less than their pKa and the corresponding hydrogel network is, therefore, swollen at $\text{pH} < \text{pKa}$ [66].

2.5 Multi-Stimuli-responsive polymers

PRPs have been extensively studied and represent one of the most explored and used stimuli-responsive polymers. pH-responsiveness associated with one, two or more stimuli have been found interesting to develop since resulting materials mimic what is currently found in nature. Most of the multiple stimuli-responsive systems were built on the basis of linear block copolymers due to their easy synthesis. Nonlinear copolymers with different stimuli-responsive behaviors may however be found [71]. Multi-stimuli-responsive materials are created with

covalently or physically bonded segments sensitive to different stimuli [6].

2.5.1 Dual-stimuli-responsive polymers (pH-, dual-stimuli-responsive polymers)

Dual-responsive polymers combine two responsive functions. The focus is on pH-, dual stimuli-responsive polymers, the second stimuli responsiveness being associated respectively to temperature, redox, light, magnetic field and glucose.

pH-, temperature-dual-responsive polymers

The main characteristics of temperature-stimuli-responsive polymers are the presence of a critical solution temperature (T_{CST}) and intermolecular interactions in aqueous medium. At T_{CST} , the temperature-responsive polymers and hydrogels exhibit a volume phase transition associated with a sudden and drastic change in the solvation state. Based on this, two categories of thermo-responsive polymers are distinguished : LCST (Lower Critical Solution Temperature) and UCST (Upper Critical Solution Temperature) [10, 72, 73]. Polymers that become insoluble upon heating, exhibit phase transition at LCST, the lowest temperature of the phase separation curve on the concentration–temperature diagram. Oppositely, polymers becoming soluble upon heating, exhibit phase transition at UCST [10]. Under the transition temperature, which is also known as cloud point (T_{CP}), polymer chains are hydrated, resulting in a clear solution. Raising the temperature higher than the clouding temperature leads to hydrophobic collapse, polymeric chains aggregation, release of solvation water molecules and finally to a cloudy solution.

Most applications of temperature-responsive polymers are related to LCST-based polymer systems. Moreover, intermolecular interactions causing hydrogel shrinkage, micelle aggregation or physical cross-links are of two types : hydrogen bonding and hydrophobic interactions. They govern reversible swelling/deswelling of hydrogels around a critical temperature [17].

pH-, temperature-responsive polymers are probably the most studied among multi-responsive polymers [74, 75]. This is due in particular to their possible multitude applications [17]. Poly (2-dimethylamino) ethyl methacrylate (PDMA), a pH-sensitive homopolymer was found to exhibit temperature responsiveness in alkaline media [76]. Moreover, this type of dual-sensitive polymer is obtained by the combination of temperature-responsive block, such as poly (*N*-isopropylacrylamide) (PNIPAM) or poly (*N*-vinylcaprolactam) (PNVCL), poly (*N,N*-diethyl acrylamide) (PDEAm), with a pH-responsive block, such as poly (acrylic acid)(PAAc), poly (methacrylic acid) (PMAAc), or poly (2-*N*-dimethyl amino ethyl methacrylate) (PDMA) [77].

Jiang et al. reported the synthesis of a dual-stimuli-responsive hydrophilic graft copolymer system ; poly (acrylic acid)-*g*-poly (*N*-vinylcaprolactam) (PAAc-*g*-PNVCL) based on the addition of a pH-sensitive moiety represented by poly (acrylic acid) (PAAc) and the thermo-sensitive one by poly (*N*-vinylcaprolactam) (PNVCL) [71]. They showed through their study the capacity of the prepared system to synergistically respond to changes in pH and temperature [71]. Monodisperse dual temperature/pH-sensitive nanoparticles have been prepared by Song et al. by distillation-precipitation polymerization using acrylic acid (AAc) and *N*-Isopropyl acrylamide (NIPAM) as monomers [78]. Yamazaki et al. [79] synthesized functional liposomes modified with methacrylate-based poly (MD-*co*-MAA-*co*-LT) copolymers. The resulting copolymer water-solubility changes in response to both pH and temperature.

pH-, redox-dual-responsive polymers

Polymeric materials exhibiting pH and redox responsiveness have been reported [80, 81]. They are basically prepared by incorporating responsive units such as disulfides, diselenides, dithienylethenes or ditellurium bonds into a pH-responsive polymer [77, 82]. In biological sys-

tems, the introduction of redox systems relies on the significantly different redox states in the circulation/extracellular fluids and intracellular compartments [82]. pH-, redox- responsive polymeric materials find great interest because tumor tissues show low pH, high temperature and highly reductive environments (higher glutathione (GSH) concentration) in comparison to normal tissues [83]. GSH is a reducing tripeptide with a thiol group (Figure 2.8) which concentration in cancer cells is 100- to 1000- fold higher than in blood and 100-fold higher than the extracellular level in normal tissues [84].

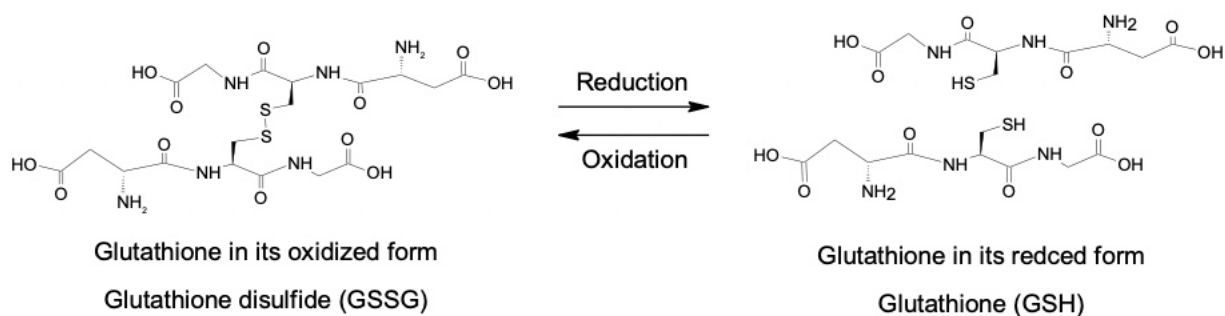


FIGURE 2.8 – Chemical structure of GSH [85]. With Copyright permission

High levels of GSH in tumor cells are known to protect the cancerous cells by conferring resistance to chemotherapeutic drugs. The ability of the GSH molecules to undergo redox reactions enables them to trigger the smart redox-responsive drug delivery systems for site-specific and controlled delivery of their payloads to intracellular targets [27].

For instance, J. John at al. produced a series of pH-, redox dual-stimuli-responsive copolymers based on pH-responsive poly (L-histidine) (PHIS)_n block and a biocompatible phospholipid analog poly (2- methacryloyloxyethyl phosphorylcholine) (PMPC) block [86] or associated with a polyurethane (PU) middle block [87]. In both cases, the pH-sensitive block(s) were connected by a redox-responsive disulfide linker. The dual-stimuli-responsive behavior of resulting materials was examined and clearly established using UV-vis spectrophotometry and fluorescence spectroscopy. The elaborated systems were efficient for intracellular tumor-

triggered drug delivery and are good candidates for cancer therapy.

pH-, light-dual-responsive polymers

Photo-responsive polymers are macromolecules characterized by changes in their properties due to light-induced isomerization or cleavage of specific functional groups along the backbone or the side chains [88]. Light-sensitive polymers are built by incorporating photochromic groups into polymer chains able to transfer hydrophobic-hydrophilic balance during photoreaction upon illuminating with light. Several photosensitive moieties, such as *o*-nitrobenzyl esters, may undergo an irreversible transformation during irradiation whereas others can react reversibly (e.g. azo-benzenes) [89]. Responses to light-stimulus consist of changes in the refractive index, dielectric constant, redox potential, geometrical structure and luminescence properties [77]. At a macroscopic level, light exposure leads to shape deformation (bending, contraction, swimming rotation, and ciliary motion) or physical properties changes such as viscosity, hydrophilicity and permeability [90]. Photo-triggered polymers are of increasing interest for the elaboration of innovative drug delivery systems able to control drug dosage [91]. pH and light stimuli dual degradable triblock copolymer micelles were prepared by Jin et al. [92]. The resulting amphiphilic triblock copolymer poly (ethylene glycol)-*b*-poly (ethanedithiol-*o*-nitrobenzyl)-*b*-poly (ethylene glycol) (PEG-*b* -PEDNB- *b* - PEG) was designed to possess two stimuli-responsive functionalities positioned repeatedly in the main chain of the hydrophobic PEDNB block. These responsive functionalities include light-cleavable-*o*-nitrobenzyl linkages and acid-labile β -thiopropionate linkages. The functions provoke self-assembly into micelles of the material with respect to environmental conditions. Micellization behavior of the prepared copolymer in aqueous solution regulated by light and pH stimuli was also demonstrated by Meng et al. [93], Zhou et al. [94] and Xia et al. [95].

pH-, magnetic-dual-responsive polymers

Electrical or magnetic fields responsive-polymers have been investigated as a form of hydrogels to have swelling, shrinking or bending behavior in response to external fields [17]. Magnetic-responsive systems employ most often superparamagnetic iron oxide magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$) [96, 97] or “soft” metallic iron but also “hard” magnetic materials such as Co, Ni, FeN, FePt, FePd in the form of nanoparticles, magnetoliposomes, or porous metallic nanocapsules incorporated into the formulation [98, 99]. The formed particles generally undergo a reversible physical shape or size distortion under externally applied magnetic current. Magnetic moment of these “small” magnets, much larger than those of molecular magnets, allows them to be sensitive to a weak stimulus (static or alternating magnetic field) with a significant effect (movement, heat generation, magnetic or optical signal) [98].

Magnetic-responsive polymers constitute a topic of intense research due to their potential applications in biomedical, coatings, microfluidics and microelectronics fields [98]. The development of stimuli-responsive polymer-based multifunctional nanostructures helps prepare functional magnetic particles with pH-responsive copolymers and promising prospects in targeted nanocarriers' drug delivery, biomedical field with applications such as heat hubs in magnetic hyperthermia or contrast agents in magnetic resonance imaging [93, 100, 101].

pH-, glucose-dual-responsive polymers

Glucose-responsive polymer systems were introduced for insulin-controlled release. To address blood's glucose concentration issue, pH-, glucose-dual-stimuli responsiveness was found to be an interesting alternative. Traitel et al. [102] reported a glucose-responsive insulin controlled release system based on the hydrogel poly (2-hydroxyethyl methacrylate-*co*- *N,N*-dimethyl amino ethyl methacrylate), also called poly (HEMA-*co*-DMAEMA), with entrapped glucose oxidase, catalase and insulin. The exposition of the elaborated system to physiological fluids provokes glucose diffusion into the hydrogel, glucose oxidase catalyzes the glucose

conversion to gluconic acid, causing swelling of the pH-sensitive hydrogel and subsequently increases insulin release. The higher the glucose concentration in the medium, the higher and faster the swelling and release rates.

The introduction of a glucose sensitive poly (4-vinylphenylboronic acid-*co*-2-(dimethyl amino) ethyl acrylate) (P(VPBA-*co*-DMAEA) gel shell onto Ag nanoparticles makes the polymer-bound responsive to glucose with high sensitivity and selectivity at physiological pH on the basis of inorganic/-organic core shell structured hybrid nanogels [103]. A glucose and pH-responsive release system based on polymeric network capped mesoporous silica nanoparticles has also been developed by Tan et al. [104]. Poly (acrylic acid) (PAAc) brush on silica nanoparticles was obtained through surface-initiated atom transfer radical polymerization followed by glycosylation to obtain poly (acrylic acid)-*N*-acryloyl glucosamine (P(AAc-AGA)). Mesoporous channels opening/closure was then linked with the glucose concentration and the variation of pH. Another pH-, glucose-sensitive hydrogel was prepared using photopolymerization by Yin et al. [105] based on concanavalin A (a saccharide-binding lectin from jack bean) and the cationic groups of *N*-(2-(dimethyl amino) ethyl methacrylamide).

Although they are less encountered in literature, it is worth mentioning that other systems such as pH-, enzyme [106]; pH-, electrical [107]; pH-, H₂O₂ [108]; pH-, ultrasound [109] and pH-, UV [110] dual-responsive polymeric systems are developed for specific applications.

2.5.2 Triple-stimuli-responsive polymers (pH-, triple-stimuli- responsive polymers

As for dual-stimuli-responsive polymeric systems, triple-responsive systems able to respond to three different types of stimuli are gaining more attention and have been prepared and reported in literature.

pH-,thermo-, light-triple-stimuli-responsive polymers

Li et al. [111] produced pH-, thermo-, light-triple-stimuli-responsive amphiphilic polymer, poly(ethylene glycol)-block-poly(dimethyl amino ethyl methacrylate)@ 2-diazo-1,2-naphthoquinone (PEG- PDMA@DNQ) via ATRP and quaternization reaction. They found out that this amphiphilic polymer could self-assemble into spherical assemblies with hydrophobic near-infrared/ultraviolet (NIR/UV) light and base responsive DNQ moieties as the core and hydrophilic PEG and pH-, temperature responsive PDMA as the corona. A pH-, photo- and temperature-responsive copolymer synthesized throughout spiropyran functionalization has also been reported by F. Jiang et al. [112, 113]. Transmission Electronical Microscopy (TEM) and Dynamic Light Scattering (DLS) analysis revealed morphological changes of the self-assemblies under the UV light and temperature stimuli. These triple-responsive-polymeric systems have been studied for the loading and the controlled release of encapsulated molecules in response to combined stimulation. Tests realized and reported with a hydrophobic fluorescent dye (coumarin) identify NIR/UV light- and pH-responsive polymer assemblies as promising to be used as nanocarriers for precisely controlled release since it was shown that the release efficiency could be enhanced dramatically under combined stimulation.

pH-,thermo-, glucose-triple-stimuli-responsive polymers

Another well-reported triple responsive polymeric material is based on pH-, thermo-, and glucose-triple-responsiveness [114, 115]. In most cases, triple-responsive block copolymers combining pH-, thermo-, and glucose-responsiveness are synthesized by incorporating boronic acid or a diol functionality along the backbone of a thermo-responsive polymer using reversible addition-fragmentation chain transfer copolymerization technique [116, 117]. Hydrogels with temperature, pH, and glucose-responsive properties made of *N*-isopropylacrylamide (NIPAM) and 5-methacrylamido-1,2-benzoxaborole (MAAm-Bo) [114], (2-dimethyl amino) ethyl methacrylate (DMAEMA) and 3-acrylamidephenylboronic acid (AAPBA) [115] or poly(vinyl

alcohol)-*b*-poly(*N*-vinylcaprolactam) (PVOH-*b*-PNVCL) [118] attracted attention for incorporation/conjugation, transport and release of various materials such as proteins, dyes, and drug molecules. Thereby they constitute promising new theranostic platforms since chemotherapeutic moieties and also diagnostic agents can be incorporated together via reversible crosslinking in these hydrogels [118]. Moreover, experimental results suggested that such multi-responsive hydrogels are highly attractive in terms of self-regulated drug delivery, as well as in other applications such as actuators, regulators, and separation systems with sensitivity to glycol [115].

pH-,thermo-, salt-triple-stimuli-responsive polymers

Vural Bütün et al. [119, 120] prepared a series of cationic diblock copolymers that exhibit reversible pH-, salt-, and temperature-induced micellization in aqueous medium from selective quaternization or betainization of 2-(dimethyl amino) ethyl methacrylate residues using respectively methyl iodide and benzyl chloride or 1,3-propane sultone under mild conditions.

Other examples of triple stimuli-responsive polymeric materials are pH-, thermo-, ionic strength-triple-stimuli polymers [121]; pH-, thermo-, CO₂-triple-stimuli polymers [122, 123]; pH-, photo-, redox-triple-stimuli polymers [124]; and pH-, glucose-, redox-triple-stimuli polymers [125].

Moreover, there are polymeric systems responsive to more than 3 stimuli. Tuncer et al. [126] prepared microgels of a water-soluble monomer, 2-(*N*-morpholino) ethyl methacrylate via emulsion polymerization that exhibit a multi-responsive behavior by responding to solution pH, temperature, ionic strength, type of dispersing media, and magnetic field. Z. Cao et al. [127] reported the synthesis of a quadruple-stimuli-responsive block copolymer sensitive to pH, temperature, light, and reducing agents thanks to TEM and DLS analysis. The amphiphilic diblock copolymer poly (2-nitrobenzyl methacrylate)-*SS*-poly (dimethyl

amino ethyl methacrylate) (PNBM-*SS*-PDMA) was synthesized via two steps of ATRP. The system was made of a light-responsive hydrophobic PNBM core, a pH- and temperature-responsive hydrophilic PDMA corona, and a redox-sensitive disulfide linker. Guragain et al. [128] also reported the synthesis of a quadruple stimuli-responsive polymeric system. Poly [*N*-isopropylacrylamide-*b*-sodium 2-(acrylamido)-2-methylpropane sulfonate] tagged with a spiropyran dimer at the poly(*N*-isopropylacrylamide) end (SP2-*b*-NIPAM154-*b*-AMPS148) was synthesized by RAFT polymerization and exhibited response to light, temperature, metal ions concentration and pH. Thermo-responsiveness was conferred to the overall block copolymer by the NIPAM154 block, metal ion responsiveness by AMPS148 block, and light- and thermo-responsiveness by the photochromic spiropyran moiety. These quadruple stimuli-responsive block copolymer micelles are expected to open up new applications in a variety of fields.

2.6 Application of pH-Responsive polymers

2.6.1 Drug delivery

In biological systems, cellular functions are regulated by biomacromolecules sensitive to changes within the local physiological environment [129]. Synthetic polymers are good tools as biomimetic agents, they are able to adapt and react to biological complex environments [6, 130]. Among useful polymers in medicine, pH-sensitive polymers are largely employed. This is mainly due to the pH variation alongside the gastrointestinal (GI) tract of the human body. In fact, pH varies from very acidic to physiological pH values in the human body [131](Table 2.1). pH variations are also observed in other body sites, e.g. cellular compartments such as vagina, extracellular and endosomal/lysosomal microenvironments or even skin [66, 132, 133]. Moreover, the pH difference between normal and cancer tissues is exploited in the therapeutic solutions of the disease [134]. Indeed, as a result of the active metabolism of tumor cells, the tumor microenvironment is highly acidic compared to normal tissues [135].

Tissue or cellular compartment	pH range or value
Saliva	6.0-7.0
Blood/Plasma	7.35-7.45
Stomach	1.0-3.0
Pancreatic fluid	8.0-8.3
Bile	7.8
Duodenum	4.8-8.2
Colon	7.0-7.5
Early endosome	6.0-6.5
Late endosome	5.0-6.0
Lysosome	4.5-5.0
Golgi	6.4
Vagina	3.8-4.5
Inflamed tissue/wound	3.8-4.5
Tumor, extracellular	7.2-6.5

TABLE 2.1 – pH values along gastrointestinal tract and in various tissues and cellular compartments. Adapted from [66, 10, 139].

Thus, PRPs are largely used in drug or gene delivery to target some specific organs or sites in the human body and to attend tumor cells in cancer treatment.

In the design of pH-responsive drug delivery systems, two main approaches are adopted. Organs or sites target-based approach is fulfilled by using polymers that contain ionizable groups. These ionizable groups by undergoing conformational, solubility changes or by transition between swelling/deswelling state are able to achieve a specific and controlled drug release in response to local pH variations [11, 136]. The second approach consists of linking a pH-responsive polymer with a drug throughout acid/base labile sensitive bonds. In response to pH variations, the linkages are able to break up inducing the release of the bioactive molecule from the polymer backbone [137, 136]. pH-sensitive polymer-based drug delivery systems have been formulated as nanoparticles, nanoaggregates, nanogels, nanocapsules, core-shell particles, micelles, liposomes, polymersomes, hydrogels, layer-by-layer films, and bioconjugates [138].

Enteric coating

With the development of colon delivery preparations in the early 1990s till now, enteric coated delivery systems have raised great interest by exploiting differences in gastrointestinal fluids' pH. pH-sensitive Eudragit polymers based on methacrylate and methyl methacrylate polymers are widely used as enteric coating polymers. They are great tools for oral drug delivery since they showed the capacity to improve drug stability and ensure a controlled and sustainable release [140, 141]. For instance, polymethacrylates with pH-dependent dissolution [142, 143] ranging from 6.0 to 7.0 are mainly used as coating agents aimed at protecting the drug core from gastric and intestinal severe environments as illustrated on the scheme presented in Figure 2.9.

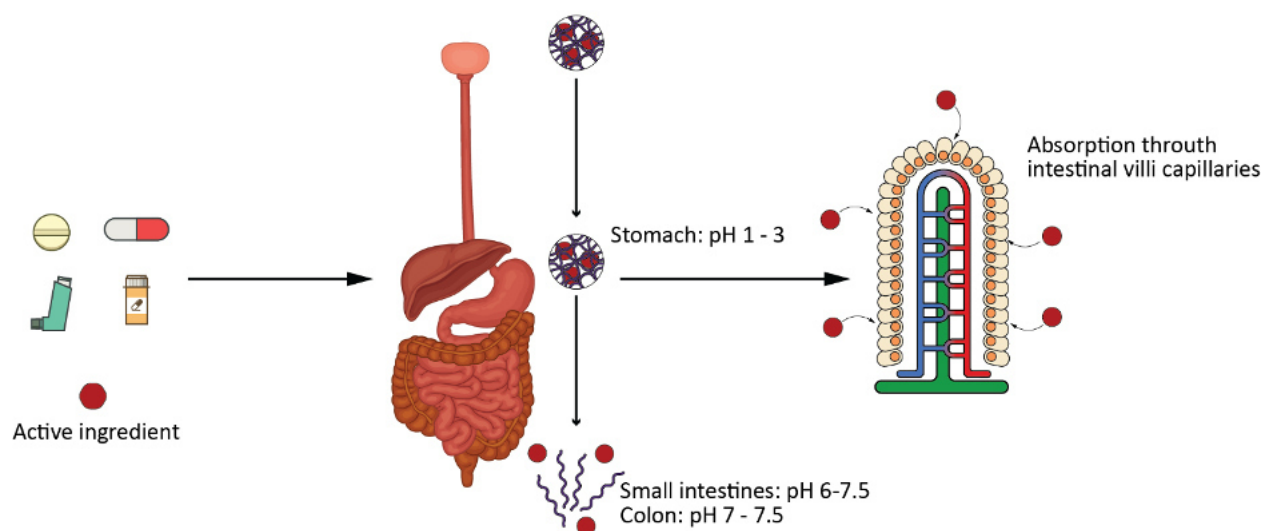


FIGURE 2.9 – Illustration of drug carried throughout the GI tract by pH-responsive polymeric matrix. The drug is protected against the acidic pH of the stomach and released in colon alkaline conditions after solubilization of the carrier. It is further absorbed to blood circulation through intestinal villi capillaries.

Enteric coating is especially useful in anti-inflammatory drug administration in the treatment of diseases like ulcerative colitis and Crohn's disease (Inflammatory Bowel Diseases) [144]. Commercially, pharmaceutical formulations already exist and are produced by Evonik Industries [145].

In terms of formulation, pH-sensitive cationic polymers are used to mask drug taste (having unpleasant qualities such as bitterness, sourness, saltiness or causing oral numbness). They are also used as drug carriers targeting the stomach by responding to its gastric low pH [139, 146]. In contrast, pH-sensitive anionic polymers responsive to intestinal high pH are used for preventing gastric degradation of drug, colon drug delivery and achieving high bioavailability of weak basic drugs [139].

Table 2.2 sums up examples of pH-responsive polymer formulations used as enteric coating materials for specific drug delivery. Among them, anti-histaminic drugs designed for enteric delivery against asthma are composed of theophylline alone or combined with another drug [147, 148, 149, 150, 151]. Salbutamol, one of the well-known and largely used anti-histaminic drug, was coated with ethyl cellulose as inner layer and Eudragit S100 (anionic copolymer based on methacrylic acid and methyl methacrylate) as outer enteric-coating polymer [152]. This formulation showed a best disintegration and dissolution profile at intestinal pH and did not dissolve at gastric pH; releasing the drug immediately in the alkaline medium. An optimized enteric-coated formulation containing 2.5%w/w of Eudragit S100 and 30%w/w of ethyl cellulose exhibited 99.04% of drug release in the intestinal medium. This enteric-coated time release formulation with suitable lag time showed interesting results in the treatment of nocturnal asthma and overcame the issues of conventional forms. Indeed, the chrono modulated therapeutically system makes possible the drug administration around 10.00 post meridiem so that after a specified lag time the drug is rapidly available in the early morning hours to treat nighttime exacerbation of the asthma condition.

H. M. Tawfeek et al. investigated the delivery of the model anti-inflammatory drug indomethacin [153]. They prepared encapsulated indomethacin within poly (glycerol-adipate-co-pentadecalactone) (PGA-co-PDL) microparticles coated with Eudragit L100-55 (anionic copolymer based on methacrylic acid and ethyl acrylate) at different ratios using an oil/water

single emulsion solvent evaporation and spray drying techniques. In vitro drug release studies suggested the possibility of anti-inflammatory colon drugs targeting through fast disintegrating tablets with a sustained release profile specifically at higher gastrointestinal pH. Other anti-inflammatory agents and their enteric coating polymeric systems are reported in Table 2.2.

Oral delivery of insulin has been boosted with the development of PRPs and enteric coating materials [154, 155, 156, 157, 158, 159, 160, 161, 162, 163]. Recently, Liu et al. [163] reported a novel type of pH- and amylase-responsive microgels prepared via aqueous dispersion copolymerization of acrylate-grafted-carboxymethyl starch (CMS-*g*-AA) and 2-isobutyl-acrylic acid (*i*BAA) as an insulin drug carrier for oral administration. The relative pharmacological availability of the insulin-loaded microgels was enhanced 2338 times compared to free-form insulin solution through oral route.

Cancer treatment

Different pH-responsive polymeric systems have been reported as potential and valuable carriers in the building of cancer diagnostics and targeted therapies. In these systems, drug release is specifically triggered by the acidic tumor environment [174]. Ionizable PRPs are widely formulated as drug delivery systems in the treatment of cancer [133, 175, 176]. In order to overcome drawbacks associated with anti-cancer agents as for example oxaliplatin (OX) which exhibits fast degradation/deactivation in the bloodstream, lack of tumor selectivity, and low bioavailability, pH-responsive drug delivery systems have been designed [177].

Promising strategies for pH controlled drug release have been developed such as the use of acid-sensitive chemical bonds or acid-labile linkers to conjugate drugs to the nanocarrier [27]. Drug delivery systems based on pH-sensitive polymers with imidazole groups, poly (β -amino ester), chemical linkages such as hydrazone, acetal, ortho ester and vinyl ester, pH-sensitive

Drug category (Disease)	Active Pharmaceutical Ingredients	pH-responsive material	Types of formulation	References
Anti-histaminic (Asthma)	Theophylline	Eudragit L100 and E100 / Gelatin	Microcapsules, Hydrogel	[147]
		Eudragit S100/ Calcium pectinate	Microspheres	[148]
		Eudragit RL100 and S100/Hydroxy propyl cellulose	Coated pellets	[149]
	Roxithromycin-Theophylline	Methylcellulose/ Sodium alginate	Microcapsules	[150]
	Piroxicam- Theophylline	Eudragit S100	Microcapsules	[151]
	Salbutamol	Eudragit S100/ Ethyl cellulose	Tablets	[152, 164]
Anti-inflammatory	Ibuprofen	Cellulose acetate phthalate	Tablets	[165]
	Loxoprofen sodium	Cellulose acetate phthalate-co-poly (methacrylic acid)	Tablets	[166]
	Diclofenac potassium/ sodium	Sodium alginate/ Acrylic acid	Hydrogel	[167]
		Eudragit L100/ PLGA	Nanoparticles	[168]
		Eudragit L00 and E100	Tablets	[169]
	Naproxen	Eudragit L100/ Hydroxy poly methyl cellulose	Microspheres	[170]
	Omeprazole	Eudragit L100-55/ Polyacrylic resin	Coated pellets	[171]
	Enrofloxacin (ENR), known as Ethyl ciprofloxacin	Ethyl cellulose/ Polyacrylic resin	Solid Lipid Nanoparticles	[172]
Insulin (Diabetes)	Insulin	Chitosan	Nanoparticles	[154, 155]
		Hydroxypropyl/ Methylcellulose phthalate	Microcapsules, Capsules	[156, 157]
		Eudragit (L30D, L100-55, FS30D, S100, L100)	Microparticles, Nanoparticles, Microspheres, Nano emulsion, vesicle	[158, 159, 160, 161, 162]
		Poly (2-isobutylacrylic acid)	Microgel	[163]
		Methacrylic acid, <i>N</i> , <i>N</i> -dimethyl amino ethyl methacrylate	Hydrogel	[173]

TABLE 2.2 – pH-responsive polymer formulations used as enteric coating materials for specific drug delivery.

cell-penetrating peptides and cationic polymers undergoing pH-dependent protonation have been studied to exploit the pH gradient along the endocytic pathway for intracellular drug delivery [139]. PRPs with acid-labile chemical bonds are tuned to remain stable at physiological pH. These acid-labile bonds are located within the polymer structure, either in the backbone (including the junctions of block copolymers) or in the side chains. The acidic environment of lysosomes, endosomes, or tumor tissues leads to destabilization and destruction of the acid-labile bonds inducing the rapid drug release. The other strategy for pH-sensitive drug release based on acid-labile bonds is to use acid-labile linkers to conjugate drugs covalently to carrier molecules or to the surface of nanostructures, forming prodrugs that are inactive until the linker is hydrolyzed [135, 178].

In cancer diagnostic or surgery, it is primordial to differentiate tumors from adjacent normal tissues [16]. pH-sensitive polymers have been used in the build-up of tumor diagnostic systems. pH-responsive polymeric micelles have been identified as contrast agents for magnetic resonance imaging (MRI) to target and, simultaneously, image cancerous tissues [179]. The mechanism is based on Fe_3O_4 loaded diblock copolymer poly (ethylene glycol)- poly (β -amino ester) (PEG-PAE) that maintains the micellar state without apparent precipitation. However, at $\text{pH} \leq 6.8$, the polymeric micelles are easily dissolved, due to the ionization of the PAE tertiary amine moieties, leading to the release and aggregation of Fe_3O_4 nanoparticles. Their gradual accumulation in acidic areas improves the accuracy of signal measurement. PEG-PAE polymeric micelle systems have also been used in association with a fluorescent dye tetramethylrhodamine isothiocyanate (TRITC) [180]. The dye showed a rapid release in weakly acidic aqueous media (pH value of 6.4). pH-sensitive polymeric systems with 10 wt.% of TRITC could deliver substantially more fluorescent dyes to the target tumor tissue in human breast tumor-bearing mice, compared to the control polymeric micelles of PEG-poly (L-lactic acid) (PEG-PLA). In order to overcome the limitations of small molecules as MRI contrast agents (CA), K. S. Kim et al. developed a cancer recognizable MRI CAs using PRPs

[181]. The cancer recognizable contrast agents (CR-CAs) with a pH sensitivity feature were self-assembled based on well-defined amphiphilic block copolymers, consisting of methoxy poly(ethylene glycol)-*b*-poly(L-histidine) (PEG-*b*-PHIS) and methoxy poly(ethylene glycol)-*b*-poly(L-lactic acid)-diethylene-tri-amino-penta-acetic acid dianhydride-gadolinium chelate (PEG-PLA-DTPA-Gd). In acidic tumoral environments (pH value below 6.5), spherical CR-CAs with a uniform size of ~ 40 nm at a physiological pH of 7.4 were destabilized due to the protonation of the imidazole groups of PHIS blocks. This protonation caused their separation into positively charged water-soluble polymers leading to a highly effective $T1$ MR contrast enhancement in the tumor region. This enabled the detection of small tumors of ~ 3 mm³ in vivo at 1.5 Tesla within a few minutes. pH-responsive polymeric fluorescent nanoprobe are able to nonlinearly amplify tumor microenvironmental signals. They are useful in the identification of tumor tissue of histological type, driver mutation, and detection of acute treatment responses quicker than conventional imaging approaches [182, 183].

Tumor poor selectivity and multidrug resistance are barriers associated with cancer treatment by chemotherapy. These drawbacks are addressed by pH-sensitive polymeric delivery systems targeting the acidic extracellular microenvironment and intracellular organelles of solid tumors [184]. The polymeric nanocarriers could avoid the use of surfactants and promote drug accumulation at the tumor sites by enhanced permeability and retention (EPR) effects [185]. Figure 2.10 presents an illustration of the microenvironment-based cancer therapy strategy.

Doxorubicin (DOX) is one of the most effective treatments in many cancer types with restrictions due to its pharmacokinetics [186]. To overcome limitations of classical chemotherapy and toxicity associated with DOX, different strategies are reported as alternatives. Among them, targeted drug delivery has shown interesting results [187, 188]. Feng et al. studied a polyelectrolyte complex composed of chitosan (Ch) and *o*-carboxymethyl chi-

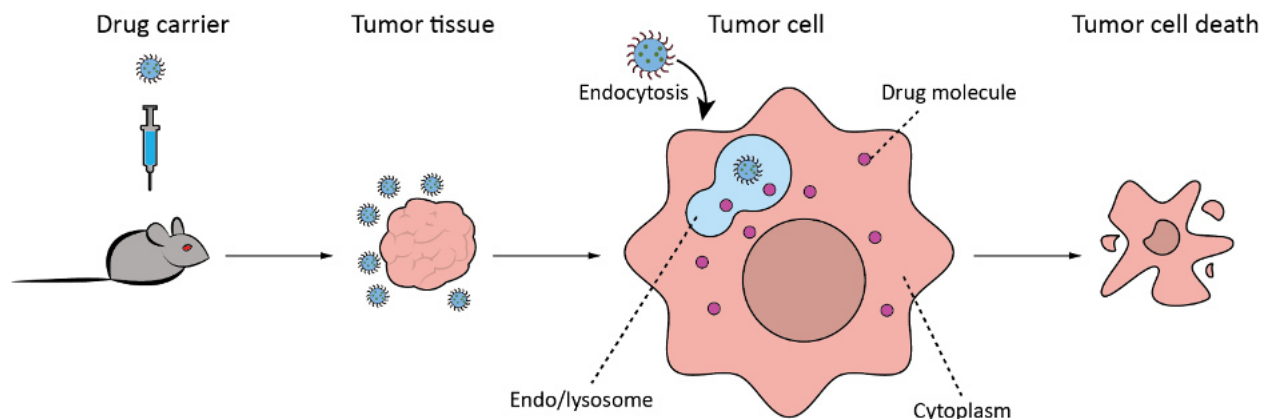


FIGURE 2.10 – Illustration of pH-responsive polymer-based tumor cells targeting, and microenvironment (pH conditions around tumor cells, low pH in endo/lysosomal compartments, GSH concentration) triggered anticancer drug release.

tosan (CMCS) as a pH-responsive carrier for oral delivery of DOX [189]. They found out that DOX's absorption throughout the small intestine, especially in jejunum and ileum was enhanced. DOX tumor targeting efficiency and therapeutic efficacy have been proved to be enhanced through pH-sensitive polymeric micelle systems or through polymer-drug conjugation via acid-labile linkages [190, 191, 192, 193, 194, 195].

One of the innovative approaches in the field of cancer treatment is the association of pH-sensitive polymers with magnetic nanoparticles [196, 197, 198]. Chitosan coated magnetic nanoparticles (Ch MNPs) provided targeting of DOX to the tumor site under a magnetic field [196]. In addition to the targeting enhancement, Montha et al. observed higher anti-cancer activity and therapeutic effect [198]. They synthesized superparamagnetic (Mn, Zn) Fe_2O_4 nanoparticles encapsulated into PLGA-coated chitosan. The releasing efficiencies of DOX by the nanocarriers were found to depend on pH. At higher concentration such as 250 g. mL^{-1} , the $\text{DOXPLGA@Ch@Mn}_{0.9}\text{Zn}_{0.1}\text{Fe}_2\text{O}_4$ showed a better anti-cancer activity to HeLa cells than that of free DOX.

Other anti-cancer agents such as Paclitaxel, Camptothacin, Tamixofen, Cisplatin have also been referenced in literature and some examples are presented with their polymeric

carriers, chemical composition and carrier structure in Table 2.3.

Gene delivery

In order to deliver nucleic acids for gene therapy, obstacles such as low stability in blood, poor cellular uptake, inefficient endosomal escape and disassembly in the cytoplasm have to be overcome. This may be addressed by using extra and intracellular stimuli including pH, redox potential, temperature, and enzyme based on the scheme illustrated in Figure 2.11. Moreover, it is known that cationic polymers are useful in complexing electrostatically negatively charged nucleic acids such as plasmid DNA (pDNA) and small interfering RNA (siRNA). In addition, the significantly reduced size and net cationic surface charge of the resulting polyplexes facilitate cellular internalization [214]. Cationic tertiary amine methacrylate-based polymers able to electrostatically interact with DNA with slight cytotoxicity are used to traffic DNA to cells since they showed a potential as gene transfer agents [11].

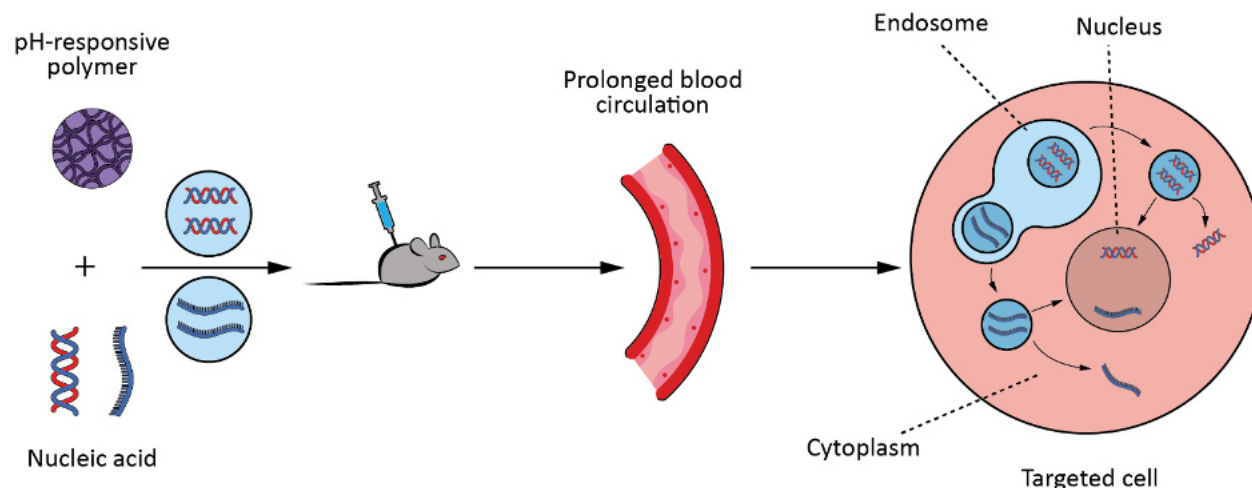


FIGURE 2.11 – Illustration of pH-responsive-based approach in non-viral gene delivery.

Polyethylenimine (PEI), cationic polymer, is one of the most widely studied gene delivery polymers. This is due to PEI high transfection efficiency in link with what is known as the proton sponge effect [215]. PEI with a molecular weight of 25 kDa named PEI25k, has been identified as standard gene carrier with recognized superiority over other polycations such as

Anti-cancer agent	Polymeric carrier structure	Polymeric system	References
Doxorubicin (DOX)	Nanoparticles	Chitosan/Carboxymethyl chitosan CS-CMCS	[189]
		Poly methacrylic acid PMAAc	[199]
		PEG-DOX-Cur prodrug, acid-labile Schiff's base linkage	[200]
	Chitosan coated magnetic Nanoparticles	Chitosan (Ch)	[196]
		PLGA-coated chitosan stabilized (Mn, Zn) Magnetic Nanoparticles	[198]
		Chitosan Dox-NPs, imine linkage	[197]
	Polymeric micelles	Poly(L-histidine)	[86]
		PHEMA- <i>b</i> -PHIS	[201]
		(HPMA)-hydrazone bonds	[191, 202]
		(HPMA)- benzoic-imine bonds	[192]
		(PEG-pH-PBLG)- orthoester linkage	[193]
		Poly (ethylene oxide)- <i>b</i> -poly (methacrylic acid) (PEO- <i>b</i> -PMAAc) copolymer	[203]
Poly (ethylene glycol)-poly (lactic acid) (<i>m</i> PEG-PLA), hydrazone linker		[204]	
Poly (ethylene glycol)- poly (2-ethoxy tetra hydrofuran-2-yloxyethyl methacrylate) PEG- <i>b</i> -PEYM, ortho ester side chains	[195]		
Paclitaxel (PTX)	Polymeric micelles	NK.105(Polyaspartic acid and PEG)	[205]
		Poly [2- (diisopropylamino) ethyl methacrylate-poly [2- (methacryloyloxy) ethyl phosphorylcholine (FA-MPC-DPA)	[206]
		Polyethylene glycol poly(<i>N</i> -acryloyloxy succinimide- <i>co</i> -butyl methacrylate <i>m</i> PEG- <i>g</i> -p(NAS-co-BMA)	[207]
Camptothacin (CPT)	Three-layered onion-structured nanoparticle	Poly [2- (<i>N</i> , <i>N</i> -diethylamino) ethyl methacrylate] (PDEA)	[208]
	Polymeric micelles	Poly (β -amino ester) methyl ether poly (ethylene glycol) (MEPG-PAE)	[180]
	Nanogel	Poly methacrylic acid (PMAAc)	[209]
Tamixofen	Nanoparticles	Chitosan	[210]
	Polymeric micelles	Poly[2-(diisopropylamino) ethyl methacrylate-Poly[2-(methacryloyloxy)ethyl phosphorylcholine (FA-MPC-DPA)	[206]
Cisplatin	Nanoparticles	Methoxy poly (ethylene glycol)-block-poly (glutamic acid) (<i>m</i> PEG- <i>b</i> -PGA)	[211]
	Nanogel	Poly (<i>N</i> -isopropyl acrylamide-methacrylic acid-hydroxy ethyl methacrylate) (P (NIPAM-MAAc-HEMA))	[212]
Gambogenic acid (GNA)	Polymeric micelles	Poly (acrylic acid)- <i>b</i> -polycaprolactone (PAAc- <i>b</i> -PCL)	[213]

TABLE 2.3 – pH-responsive polymer formulations used as anti-cancer drug carriers.

Poly L-Lysine due to its high charge density and chain flexibility [216]. Transfection efficacy and cytotoxicity of PEI have been linked to its molecular weight, suggesting that branched PEI with higher molecular weight shows high transfection and cytotoxicity [217]. In order to address drawbacks such as cytotoxicity and possible particle aggregation leading to large particles and poor diffusion in the vascular system, core-shell nanoparticles made of PEI and PMMA [218], conjugated PEI [219, 220], dendritic polyglycerol dPG-PEI nanogel platform [221] or degradable PEIs with acid-labile imine linkers and glutadialdehyde [217] were synthesized. Both approaches demonstrated the reduction of PEI toxicity and their possible application to non-viral gene delivery.

Cationic tertiary amine methacrylate-based block copolymers may also efficiently condense negatively charged biomolecules via electrostatic interactions with Poly [(2-diethylamino)ethyl methacrylate] (PDEA) considered as one of the most promising non-viral vectors for gene delivery due to its proton sponge ability [222, 223]. Once more, reduction in cytotoxicity is studied for the delivery of nucleic acids. Thus, Poly(ethylene glycol) (PEG) or Poly 2-(methacryloyloxy) ethyl phosphorylcholine (PMPC) have been used in combination with cationic polymeric non-viral vectors [224, 225, 226]. PEG modification of cationic polymers has been highlighted as a useful tool in gene delivery. Indeed, this is due to the fact that the latter provides biocompatibility and charge shielding effect to reduce nonspecific interactions of polyplexes with blood components, prolonged circulation, and low *in vivo* toxicity [227].

2.6.2 Sensing and actuation

Progress in stimuli-responsive polymers development led to the tuning of innovative colorimetric detection tools capable of giving rapid readable responses via color changes, detectable with naked eyes. Thus, colorimetric pH sensors have been developed based on PRPs [228, 229]. pH switchable zwitterionic polymers have been proposed for fast and efficient detection and control of biological (cell or bacteria) adhesion to surfaces [230] and for the

detection of Gram positive and Gram negative bacteria based on the ionic complex formation and the distinguishable fluorescence between polymers and bacteria's surfaces when treated with different pH [231].

As mentioned above, PRPs find applications in the diagnosis of tumoral systems. Hence, pH-responsive nanoprobe have been developed to respond to acidic microenvironments and help in the *in vivo* tumors visualization regardless of the tumor type or even its development stage [232]. Moreover, pH-sensitive hydrogels may be prepared for modulated insulin delivery in the treatment of insulin-dependent diabetes mellitus. To address major drawbacks of treatments associated to insulin delivery such as heaviness of insulin injection and difficulty in controlling insulin dosage [233], glucose oxidase and insulin loaded pH-responsive hydrogels present a real alternative, since the release of insulin from this system is governed by the glucose concentration in blood [102, 234].

Associated with sensing, PRPs may act as actuators based on action-reaction basis [235, 56, 236]. On the principle of innovative cancer treatment using pH-sensitive polymers associated to targeting based magnetic field with magnetic nanoparticles, Li et al. proposed a soft microrobot made of a hydrogel bilayer structure of 2-hydroxyethyl methacrylate (HEMA) and poly(ethylene glycol) acrylate (PEGDA) with iron (II, III) oxide particles (Fe_3O_4) fabricated by a conventional photolithography procedure for the delivery of anti-cancer drug microbeads constituted of polycaprolactone-docetaxel (PCL-DTX) [237]. Moreover, on-demand pH-triggered delivery nanocarriers have also been reported based on this system [238].

Interpenetrating network hydrogel bilayers made of poly (*N*-isopropylacrylamide) (PNIPAM) in the presence of positively charged polyelectrolyte poly (diallyl dimethyl ammonium chloride) (PDADMAC) or poly acrylic acid (PAAc) showed directional bending in response to stimuli such as pH, thanks to swelling and shrinking upon pH variations [239, 240]. These

elaborated hydrogels exhibit reversible bidirectional changes or complex 3D deformation in response to pH, temperature or ionic strength. They may be used in the production of soft grippers for the loading and release of small molecules, multi-responsive flexible materials, with potential applications in soft robots, actuation, and sensing. Moreover, addition of an acid-based pH-indicator to a bilayer-type hydrogel composite with poly (2-(dimethyl amino) ethyl methacrylate) (PDMA) as first layer and poly (2-(dimethyl amino) ethyl methacrylate)-acrylamide (PDMA-AM) as second layer, combined with sodium alginate as the interpenetrating polymer may provide a visible color change simultaneous to shape changes when immersed in acidic environment. This provides possibilities in the application of environmental sensors on account of visual recognition [241].

J. Y. Park et al. fabricated pH-responsive-based microspheres that act as microfluidic valves replacing classical actuating components [242]. Acrylic acid was integrated to a former poly(dimethylsiloxane) valve. The microspheres regulate fluid circulation on an open/close basis according to pH changes thanks to swelling and shrinking associated to pH (Figure 2.12).

L. D. Zarzar et al. produced a chemo-mechanical hybrid actuation system composed of passive structural skeletal elements put in motion by a poly (AAc-*co*-AAm) hydrogel muscle that swells and contracts in response to chemical signals. This system enables pH-responsive reversible motion of microstructures in liquid [243]. The authors demonstrated the patternable actuation of polymeric microposts controlled by a structured layer made of the prepared hydrogel. Electrochemically generated pH gradients allow visualization of hydrogel volume-phase transition and how this translates to movements of the microstructures. Indeed, the AAc is ionized at $\text{pH} > 4.25$, which leaves the hydrogel polymer backbone with a net charge. Dissociated hydrogen ions remain in the hydrogel to balance this negative charge, which in turn cause increased osmotic pressure, ultimately leading to water infiltration and hydrogel swelling. At $\text{pH} < 4.25$, the acrylate is protonated, the osmotic pressure is decreased, water is

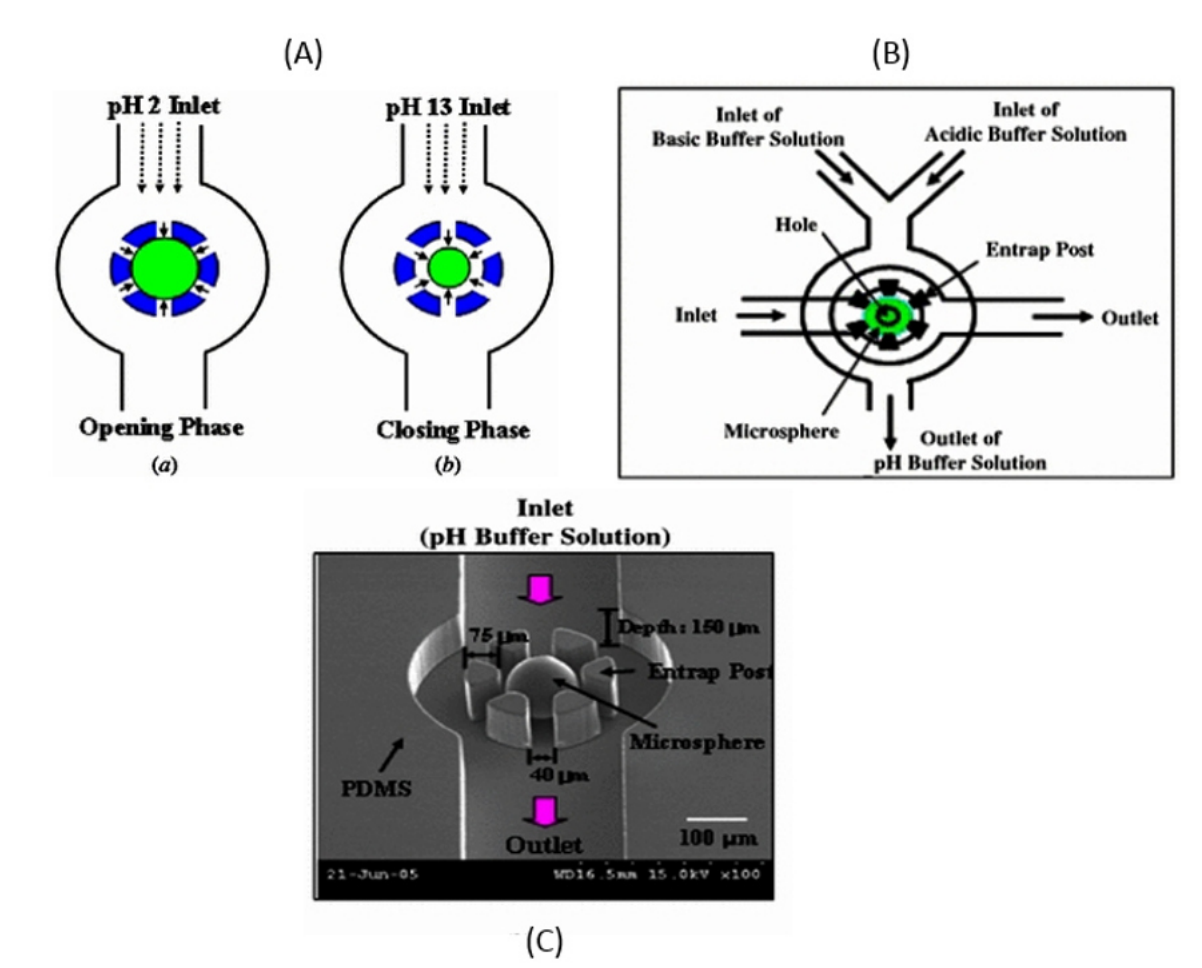


FIGURE 2.12 – Illustration showing the fabricated microvalve's 'OPEN' and 'CLOSE' operations. The microsphere shrinks and the channel is opened at the appearance of acidic solution, while the channel is closed at the appearance of basic solution. (A) Schematic diagram showing the motion of (a) the acidic solution around the entrapped microsphere at the start of the opening phase and (b) the basic solution around the entrapped microsphere at the start of the closing phase. (B) Schematic diagram of pH-responsive microvalve seen from the top view. (C) SEM image of the produced microspheres [242]. With Copyright permission

expelled, and the hydrogel contracts. The volume-phase transition of the pH-responsive hydrogel drives the actuation of the embedded microstructures as it can be seen in Figure 2.13.

2.6.3 Surfaces functionalization and membranes

Stimuli-responsive polymers emergence has boosted the research on environmental - responsive membranes (ERM). These membranes have been till now prepared by processes like

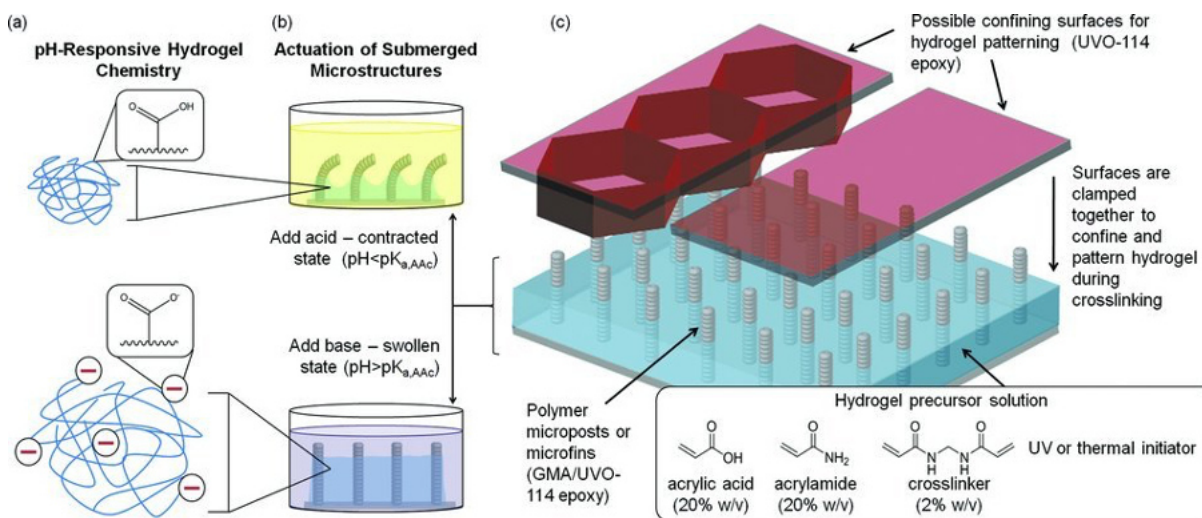


FIGURE 2.13 – **a)** Hydrogel response to pH. **b)** Actuation of microstructures embedded in hydrogel submerged in aqueous solution colored with bromophenol blue indicator. **c)** Overview of the fabrication of pH-responsive hydrogel-embedded polymer micro-structures with topographically patterned hydrogel. The confining surface can have any arbitrary pattern [243]. With Copyright permission

surface graft polymerization of weak polyelectrolyte chains onto a support membrane [244]. For ERM preparation, poly (vinylidene fluoride) (PVDF) membrane is the most commonly used material [245]. By grafting PRPs such as poly [2-(diethyl amino) ethyl acrylamide] (PDEAm) [245], poly (methacrylic acid) (PMAAc) [244] or poly acrylic acid (PAAc) [246] to this membrane, it has been shown that resulting membranes exhibit pH-dependent performances in the separation of different feeding stream components. For instance, Y. Xian et al. [247] showed a variation of separation efficiency for separating hexadecane/water emulsion depending on temperature and pH with separation efficiencies of 97.10% at 25°C under neutral condition and 30.26% at 50°C under alkaline condition. pH-sensitive ERM can be used in oil/water emulsion separation, oil recovery, removal process of specific species such as heavy metals from feed water streams by chemical binding, wastewater treatment, and microfluidic devices. Further promising applications such as membrane antifouling may be also considered.

Poly(4-vinylpyridine) (P4VP) based porous membranes are able to respond to pH fluctuations throughout self-adjustment of their size with the changes of outside pH stimulus

through the protonation and deprotonation of internal pyridine groups [248, 249]. Thus, this functionalization confers to the membranes a gate-controlled water permeability which is exploitable in separation systems such as porous microfiltration. Recently, J. D. Willot introduced a novel water-based phase inversion approach named aqueous phase separation (APS) for the synthesis of a poly(4-vinylpyridine) (P4VP) based porous membrane films [249]. The synthesis approach gives a certain degree of control over membrane structure leading to symmetric porous microfiltration membranes and asymmetric dense nanofiltration membranes, effective cleaning of the membrane without the use of harsh or chemicals, and advanced membranes with responsive properties without any use of toxic solvents.

Moreover, these pH-responsive ERM exhibited self-cleaning properties and high regeneration performances.

2.6.4 Chromatography, electrophoresis and extraction

Stimuli-responsive materials including PRPs have been used in various separation and purification technologies such as extraction, electrophoresis and chromatography [250].

Biomolecules of interest have been extracted from different mixtures using pH-responsive matrices. pH-responsive hydrogels demonstrated their utility in the high and fast adsorption or swelling and uptake of heavy metal ions such as Pb^{2+} , Cd^{2+} , Ni^{2+} , Cu^{2+} , Fe^{2+} , Zn^{2+} , Cr^{3+} [251, 252, 253], of bovine serum albumin protein (BSA) [254, 255] or β -blocker atenol [256]. Moreover, different pH-responsive systems have been used as remarkable tools in the building of packing materials of stationary phase in ion-exchange chromatography [257, 258, 259, 260, 261, 262].

Changes in pH and temperature as a second stimulus lead to the establishment of optimal operating conditions for an improved separation of different biomolecules of interest.

It was proved that interactions between the solute and the stationary phase could be freely controlled by temperature and pH [258]. The use in most cases of only aqueous solutions as mobile phase without organic solvent confers this selective separation method a green and sustainable character. Table 2.4 summarizes various pH-responsive based systems found in literature for extraction or used as packed materials for chromatography stationary phase.

2.6.5 Other applications

Nanoparticles synthesis within amphiphilic block copolymer micelle cores has been explored. Indeed, these block copolymer cores used as stabilizers may act as nanoreactors for metal (especially catalytic) particle's nucleation and growth with the advantages of enhancing the control of particle size and stability [268, 269, 270, 271]. Moreover, pH-responsive microgel pores may also be used as templates or nanosized reactors for the synthesis of inorganic nanoparticles [272]. Elaborated PRPs have also been employed as flocculants since they proved to induce substantial reversible flocculation and sedimentation with pH variations [273, 274]. Thus, these pH-responsive materials could find application as flocculation agents in various industrial fields such as clarifying industries or separation processes. Table 2.5 summarizes some other applications involving PRPs.

2.7 Concluding remarks and future perspectives

Stimuli-responsive polymers have been largely studied in the last two decades due to their unique properties to adapt sharply and reversibly to their surrounding environment by exhibiting alteration of their structure and/or physical properties. Polymers sensitive to different stimuli such as pH, temperature, light, electrical or magnetic field and ionic strength have been elaborated and investigated. In the present review, the focus was on pH-responsive polymers (PRPs). An origin-based and functional group-based classification of the most com-

pH-responsive polymers	Stimuli	Application/ Type of separation	Targeted molecules	References
Poly (vinylpyrrolidone) VP or <i>N</i> -vinyl-2-pyrrolidone-co-methylacrylate P(VP- <i>co</i> -MA)	pH	Hydrogel based adsorption	pH-dependent Heavy metals separation Cu ²⁺ , Cd ²⁺ , Ni ²⁺ and Zn ²⁺	[252]
Poly (acrylic acid-ethylene glycol dimethacrylate) [poly(AAc-EGDMA)]	pH	Hydrogel, Solid phase extraction	Atenol	[256]
<i>N,N</i> -(dimethyl amino) ethyl methacrylate (DMAEMA)	pH	Hydrogel, Water-sorption and metal-uptake	pH-dependent metal separation ; Cu ²⁺ , Ni ²⁺	[251]
2-hydroxyethyl acrylate (HEA) and 2-acrylamido-2-methylpropane sulfonic (AMPS) ; HEA/AMPS copolymer hydrogel	pH - temperature	Hydrogel based, adsorption	pH-dependent heavy metals separation ; Pb ²⁺ , Cd ²⁺ , Cr ³⁺ , and Fe ³⁺	[253]
Poly (<i>N</i> -iso propyl acrylamide) (PNIPAM)- carboxy methyl cellulose (CMC)	pH-temperature	Hydrogel based ; adsorption	pH dependent bovine serum albumin (BSA)	[254, 255]
PMMDN polymer [Methyl acrylic acid (MAA), Methyl methacrylate (MMA), Methacrylic acid 2-(dimethyl amino) ethyl ester , <i>N</i> -Methylolacrylamide (<i>N</i> -MAM)(Dimethyl amino) ethyl ester, <i>N</i> -Methylolacrylamide (<i>N</i> -MAM)]	pH	Affinity precipitation	Lysosome, microbial transglutaminase	[263, 264]
Poly (AAc- <i>co</i> -hydrazide)	pH	Polymeric matrix enrichment	Glycopeptides	[265]
<i>N</i> -isopropylacrylamide (NIPAM) and 4-vinylphenylboronic acid (p-VPBA)	pH-temperature	Macroporous imprinted cryogels	Ovalbumin	[266]]
Glycidyl methacrylate- <i>co</i> -ethylene dimethacrylate) (Poly(GMA- <i>co</i> -EDMA))	pH	Stationary phase, monolithic column	Proteins separation (human immunoglobulin G, α -chymotrypsinogen A, cytochrome C and lysozyme	[267]
Poly (acrylic acid- <i>co</i> -butyl acrylate) (AAc- <i>co</i> -BA)	pH	Reverse phase liquid chromatography (RPLC) - Hydrophilic interaction chromatography (HLIC)	Sulfonamides, soybean isoflavones, and nucleotides	[261]
Poly (2-dimethyl amino ethyl methacrylate)- block- poly-(acrylic acid) (PDMA- <i>b</i> -PAAc)	pH, Temperature and ionic strength	Ion exchange HPLC	Low molecular weight acidic, basic and neutral analytes, biomolecules such as proteins (horse heart myoglobin, hen egg white lysozyme, and bovine heart cytochrome c)	[262]
Poly (NIPAM- <i>co</i> -BMA- <i>co</i> -DMAPAAm) Terpolymer	pH-temperature	Ion exchange Reverse phase HPLC	Phospho-tyrosine, phosphopeptide and oligonucleotides	[260]
<i>N</i> -iso propyl acrylamide (NIPAM), butyl methacrylate (BMA) and <i>N,N</i> -dimethylaminopropyl acrylamide (DMAPAAm), Poly (NIPAM- <i>co</i> -BMA- <i>co</i> -DMAPAAm)	pH- temperature	Ion exchange HPLC	Nonsteroidal anti-inflammatory drugs (ibuprofen, ketoprofen, naxopren)	[259]
<i>N</i> -isopropylacrylamide- <i>co</i> - <i>N</i> -tert-butyl acrylamide- <i>co</i> -acrylic acid, P (NIPAM- <i>co</i> -tBAAm- <i>co</i> -AAc)	pH-Temperature	Ion exchange HPLC	Organic acids and phenylthiohydantoin-amino acids, Melatonin	[257, 258]

TABLE 2.4 – pH-responsive based systems for extraction or used as packed materials for chromatography stationary phase.

Applications	pH-responsive polymer	References
Stabilizers (Synthesis of metal nanoparticles)	Poly (hexa (ethylene glycol) methacrylate)-block-poly (2-(diethyl amino) ethyl methacrylate); (PDEA- <i>b</i> -PHEGMA) micelles	[269]
	Poly (styrene)-block-poly (4-vinylpyridine)(PS- <i>b</i> -P4VP micelles)	[270]
	Poly (ethylene oxide)-block-poly (2-vinylpyridine) (PEO- <i>b</i> -P2VP micelles), Poly (hexa (ethylene glycol) methacrylate)-block-poly (2-(diethylamino)ethyl methacrylate) (PHEGMA- <i>b</i> -PDEA micelles), PEO- <i>b</i> -PDEA micelles	[271]
	Poly (2-(diethylamino)ethyl methacrylate) (PDEA microgels)	[272]
	Poly (2-vinylpyridine) (P2VP, brushes)	[275, 276]
Flocculants	4-vinylpyridine grafted to Cellulose graft, Nano-crystals	[273]
	Temperature and pH responsive Starches (TPRS)	[274]
Sol fertilizer	Polydopamine-graft-poly (acrylic acid) (Pdop- <i>g</i> -PAAc polymer brushes)	[277]

TABLE 2.5 – Some other pH-responsive polymer applications.

monly cited polyacids and polybases PRPs is provided first. Progress made to develop new PRPs or systems promoted their use as drug, gene and active compound delivery systems, tumor tissue targeting and cancer treatment. Moreover, they find application in many other domains such as sensing, actuation, surfaces functionalization and selective membranes. PRPs present different structures/architectures and their self-assembly behavior allows the design of various nanostructures such as shell/core cross-linked micelles, hollow spheres, hydrogels, microgels, layer-by-layer nanofilms that have showed their utility notably in drug delivery systems. However, many challenges remain to be addressed. pH-responsive polymer potential applications are still limited probably due to the few pH-sensitive environments. Moreover, not all laboratory developed to date pH-responsive drug delivery systems have already been industrially produced and commercialized due to human body specifications and cytotoxicity concerns mainly. The same remark can be made for pH-responsive based sensing, actuator or separation devices. In this context, multi-responsive materials in general and polymers in particular are important to develop since they are able to mimic what is commonly observed in nature.

Multiple stimuli responsive properties have been used in the design of drug delivery vehicles for the controlled release of drugs *in vivo*. A well-known example is the combination of pH and redox responsiveness to target intrinsic environment of malignant cancer cells rather than healthy ones [278]. However, it can be noticed that most of dual responsive polymeric materials in drug delivery are intended for anticancer drugs with few reports on other classes of drugs that can also benefit from these advances [279].

Recently, new application domains of PRPs are reported. For instance, this is the case of the food industry. In fact, recent studies suggest pH-responsive polymeric films as smart packaging materials for real-time food freshness monitoring [280, 281, 282]. In addition, the designed pH-responsive films exhibit antioxidant activity [283, 284], antimicrobial activity [285, 286], or both [46, 287] making them sweet for food preservation. Apart from their functionalities, the attractiveness of these systems resides in their non-toxicity for consumers. This paves the way to edible PRPs development with antimicrobial and antioxidant activities and to functional foods with pH-responsive property [288].

Notes

The authors declare no conflict of interest

ABBREVIATIONS

AAc, Acrylic acid ; **AAm**, Acrylamide ; **AAPBA**, 3-acrylamidephenylboronic acid ; **AGA**, *N*-acryloyl glucosamine ; **AMPS**, 2-(acrylamido)-2-methylpropane sulfonate ; **APS**, Aqueous phase separation ; **ATRP**, Atom transfer radical polymerization ; **b**, block ; **BA**, Butyl acrylate ; **BMA**, Butyl methacrylate ; **BSA**, Bovine serum albumin ; **CA**, Contrast agent ; **Ch**, Chitosan ; **CMC**, Carboxymethyl cellulose ; **CMCS**, Carboxymethyl chitosan ; **CMS**,

Carboxymethyl starch ; **CPT**, Camptothacin ; **CR-CA**, Cancer recognizable contrast agent ; **Cur**, Curcumin ; **DLS**, Dynamic Light Scattering ; **DMAEA**, 2-(dimethyl amino) ethyl acrylate ; **DMAEMA**, *N, N*-dimethyl amino ethyl methacrylate ; **DMAPAAm**, *N,N*-dimethyl amino propyl acrylamide ; **DNA**, Deoxyribonucleic acid ; **DNQ**, 2-diazo-1,2-naphthoquinone ; **DOX**, Doxorubicin ; **dPG**, Dendritic polyglycerol ; **DTPA**, Diethylene-tri-amino-penta-acetic acid dianhydride ; **EDMA**, Ethylene dimethacrylate ; **EGDMA**, ethylene glycol dimethacrylate ; **EPR**, Enhanced permeability and retention ; **ERM**, Environmental-responsive membranes ; **FA**, Fumaric acid ; **g**, graft ; **Gd**, Gadolinium ; **GI**, Gastrointestinal tract ; **GMA**, Glycidyl methacrylate ; **GSH**, Glutathione ; **GTP**, Group transfer polymerization ; **HA**, Hyaluronic acid ; **HEA**, 2-hydroxyethyl acrylate ; **HEMA**, Hydroxyethyl methacrylate ; **HLIC**, Hydrophilic interaction chromatography ; **HPLC**, High performance liquid chromatography ; **HPMA**, *N*-(2-hydroxypropyl) methacrylamide ; **HPMC**, Hydroxypolymethylcellulose ; **iBAA**, 2-isobutyl-acrylic acid ; **kDa**, Kilodalton ; **LCST**, Lower Critical Solution Temperature ; **MA**, Methyl acrylate ; **MAA**, Methyl acrylic acid ; **MAAc**, Methacrylic acid ; **MAAm-Bo**, 5-methacrylamido-1,2-benzoxaborole ; **MEPG**, Methyl ether poly (ethylene glycol) ; **MMA**, Methyl methacrylate ; **MNP**, Magnetic nanoparticle ; **MPC**, 2-Methacryloyloxyethyl phosphorylcholine ; **mPEG**, Methoxy poly (ethylene glycol) ; **MRI**, Magnetic resonance imaging ; **N-MAM**, *N*-Methylol acrylamide ; **NAS**, *N*-(acryloyloxy) succinimide ; **NIPAM**, *N*-isopropylacrylamide ; **NIR/UV**, Near infrared/Ultraviolet ; **NMP**, Nitroxide-mediated polymerization ; **NP**, Nanoparticle ; **OX**, Oxaliplatin ; **P2VP**, Poly (2-vinylpyridine) ; **P4VP**, Poly (4-vinylpyridine) ; **PAAc**, Polyacrylic acid ; **PAAPBA**, Poly (3-acrylamidophenyl boronic acid) ; **PAE**, Poly (β -amino ester) ; **PAM**, Polyacrylomorpholine ; **PAMAM**, Poly (amidoamine) dendrimer ; **PAMPS**, Poly (2-acrylamido-2-methylpropane sulfonate acid) ; **PASA**, Poly (aspartic acid) ; **PBLG**, Poly (γ -benzyl L-glutamate) ; **PCL**, Polycaprolactone ; **PDADMAC**, Poly (diallyl dimethyl ammonium chloride) ; **PDEA**, Poly (2-diethyl amino) ethyl methacrylate ; **PDEAm**, Poly (2-diethyl amino) ethyl acrylamide ; **PDL**, Poly pentadecalactone ; **PDMA**, Poly (2-dimethyl amino) ethyl methacrylate ; **PDMA-AM**,

Poly (2-(dimethyl amino) ethyl methacrylate)-Acrylamide; **PDMAEA**, Poly ((2-dimethyl amino) ethyl acrylate); **PDMAPMAm**, Poly (*N*-(3-dimethyl amino) propyl) methacrylamide; **pDNA**, Plasmid deoxyribonucleic acid; **Pdop**, Polydopamine; **PDPA**, Poly (2-diisopropylamino) ethyl methacrylate; **PDPAEMA**, Poly (2-dipropyl amino) ethyl methacrylate; **PEDNB**, poly (ethanedithiol-@-nitrobenzyl); **PEG**, Polyethylene glycol; **PEGAP**, Poly (ethylene glycol acrylate phosphate); **PEGDA**, Poly (ethylene glycol) acrylate; **PEGMP**, Poly (ethylene glycol methacrylate phosphate); **PEI**, Polyethylenimine; **PEO**, Poly (ethylene oxide); **PEPyM**, Poly (*N*-ethylpyrrolidine methacrylate); **PEYM**, Poly (2-ethoxy tetra hydrofuran-2-yloxyethyl methacrylate); **PGA**, Poly (glycerol-adipate); **PHEGMA**, Poly hexa (ethylene glycol) methacrylate; **HEMA**, Poly hydroxyethyl methacrylate; **PHIS**, Poly (histidine); **PIA**, Poly (itaconic acid); **PImHeMA**, Poly (6-(1-Himidazol-1-yl) hexyl methacrylate); **PKSPMA**, Poly (2-acrylamido-3-sulfopropylmethacrylate potassium salt); **PLA**, Poly (L-lactic acid); **PGA**, Poly (L-glutamic acid); **PLGA**, Poly(lactide-co-glycolide); **PMAAc**, Polymethacrylic acid; **PMEMA**, Poly(2-*N*-morpholino) ethyl methacrylate; **PMEMAm**, Poly(2-*N*-morpholino) ethyl methacrylamide; **PMMA**, Poly methyl methacrylate; **PMPC**, Poly (2-methacryloyloxy ethyl phosphorylcholine); **PNBM**, Poly (2-nitrobenzyl methacrylate); **PNIPAM**, Poly (*N*-isopropylacrylamide); **PNVCL**, Poly (*N*-vinyl caprolactam); **PPAAc**, Polypropylacrylic acid; **PPI**, Poly (propylenimine) dendrimer; **PS**, Poly styrene; **PSSA**, Poly (4-styrenesulfonic acid); **PtBAEMA**, Poly (2-ter-butylamino) ethyl methacrylate; **PTX**, Paclitaxel; **PVBA**, Poly (4-vinylbenzoic acid); **PVBPA**, Poly (4-vinyl-benzyl phosphonic acid); **PVDF**, Poly (vinylidene fluoride); **PVI**, Poly (*N*-vinylimidazole); **PVOH**, Poly (vinyl alcohol); **PVP**, Poly vinylpyrrolidone; **PVPA**, Poly (vinylphosphonic acid); **PVPBA**, Poly (vinylphenyl boronic acid); **PVSA**, Poly (vinylsulfonic acid); **RAFT**, Reversible addition fragmentation chain transfer polymerization; **RNA**, Ribonucleic acid; **RPLC**, Reverse phase liquid chromatography; **SFRP**, Stable free-radical polymerization; **SiRNA**, Small interfering ribonucleic acid; **tBAAm**, tert-butyl acrylamide; **T_{CP}**, Cloud point; **T_{CST}**, Critical solution temperature; **TEM**, Transmission

electron microscopy ; **TRITC**, Tetramethylrhodamine isothiocyanate ; **UCST**, Upper Critical Solution Temperature ; **VPBA**, 4-vinylphenylboronic acid.

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PARTIE EXPERIMENTALE

Nous nous sommes proposés dans ce travail expérimental de préparer en solution des particules pH-sensibles et stables des copolymères Eudragit E100 (copolymère de diméthylaminoethyl méthacrylate, butyle méthacrylate et de méthyl méthacrylate dans un rapport 2 :1 :1) et Eudragit L100 (copolymère d'acide méthacrylique et de méthyl méthacrylate dans un rapport 1 :1). Ces polymères, biocompatibles, largement utilisés, sont très peu coûteux, faciles d'accès et à manipuler et rentrent parfaitement dans le contexte de l'étude que nous nous sommes proposés d'effectuer. Ils sont principalement employés dans l'encapsulation et la protection de substances actives destinées à une libération ciblée et contrôlée au niveau de l'organisme humain. Le travail expérimental que nous présentons est subdivisé en trois parties. Ces trois parties présentent les différentes études expérimentales menées et déclinées sous la forme d'articles de recherche. La première partie est consacrée à l'étude des conditions de solubilisation et de précipitation des deux copolymères. L'influence de divers paramètres physico-chimiques sur la stabilité colloïdale des particules préparées en solution y est abordée et les particules obtenues ont été caractérisées en termes de taille, distribution de taille, de potentiel zêta et de morphologie. Dans une seconde partie, l'influence d'additifs (polyélectrolytes secondaires) et leur effet sur les propriétés colloïdales des particules préparées sont traités. Les particules préparées sont également caractérisées en termes de distribution de taille, de potentiel zêta et de morphologie. La formation de complexes polyélectrolytiques ou polyplexes impliquant les Eudragit y est abordée. Dans la troisième partie de cette étude expérimentale, nous abordons les interactions ayant lieu en solution entre les deux copolymères et les différentes catégories de tensioactifs. Les tensioactifs ; non ionique, zwitterionique, ionique (anionique et cationique) y sont notamment étudiés. La formation de complexes Eudragit-tensioactif est discutée dans cette troisième partie. Ces complexes sont caractérisés en termes de taille et de potentiel zêta.

Chapitre 3

CARACTERISATION PHYSICO-CHIMIQUE DES EUDRAGIT E100 ET L100

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Cette première étude expérimentale [1] porte sur les conditions de solubilité et de précipitation des copolymères Eudragit E100 et L100, deux copolymères sensibles au pH. Si ces deux copolymères sont utilisés depuis de nombreuses d'années dans l'encapsulation de molécules actives en vue de leur protection et/ou de leur libération ciblée [2], il est ressorti de notre étude bibliographique que les conditions opératoires pour leur solubilisation/précipitation n'étaient pas clairement établies. Partant des données de la littérature où nous avons pu voir que les Eudragit E100 et L100 sont solubles respectivement à des valeurs de pH inférieures et supérieures à 6 [2, 3, 4], nous avons procédé à une étude systématique de solubilisation et de précipitation de ces deux Eudragit. En ce qui concerne les dispersions obtenues suite à la précipitation des copolymères, celles-ci ont été caractérisées en termes de distribution de taille de particules, de potentiel zêta et de morphologie. Pour finir, une titration des fonctions amines et carboxyliques respectivement des Eudragit E100 et L100 est réalisée.

Pour l'Eudragit E100, la solubilité a été étudiée sur une gamme de pH allant de 0 à 6. En ce qui concerne l'Eudragit L100, l'étude de solubilité a porté sur une gamme de pH allant de 6 à 14. Ces études de solubilité ont été réalisées aussi bien dans des solutions d'acide chlorhydrique (E100) et de soude (L100) que dans des solutions tampons. L'étude de la précipitation des Eudragit E100 et L100 a été réalisée respectivement par basification ou acidification directe de solution de polymère sous agitation mécanique. La distribution de taille des particules a été obtenue par diffusion dynamique de la lumière via un Zetasizer Nano ZS (Malvern Instruments) pour les dispersions submicroniques et par diffraction de la lumière au Mastersizer 3000 (Malvern Instruments) pour les dispersions micrométriques. Le potentiel zêta des particules préparées pour les différentes dispersions obtenues a été mesurée par déduction de la mobilité électrophorétique. Les mesures de potentiel zêta ont été réalisées pour une valeur de salinité et de pH donnée, les particules préparées étant sensibles au pH du milieu. La morphologie des particules préparées a été observée en microscopie électronique par transmission. L'influence de divers paramètres tels que le pH du milieu, la salinité, la

concentration en polymère, et du temps d'incubation sur la solubilisation et la précipitation des Eudragit E100 et L100 est également traitée.

La première observation ayant été réalisée est que les deux polymères induisent une modification du pH du milieu. Cette modification de pH est d'autant plus importante que la concentration en polymère est élevée. Ceci constitue une remarque importante dans la mesure où la solubilité des deux copolymères étudiés dépend du pH final du milieu, une fois l'équilibre atteint. Nous avons donc pu établir que la solubilité des Eudragit E100 et L100 est gouvernée par une action synergique du pH final (ou initial) du milieu, de la concentration en polymère et du temps d'incubation. L'incidence du copolymère et de sa concentration sur le pH du milieu constitue un des points saillants de cette étude, cette observation n'étant pas rapportée dans les études où les Eudragit E100 et L100 sont employés à des fins de revêtement ou d'encapsulation. Il est connu que les polyélectrolytes sont solubles sous leur forme ionisée. Dans le cas de l'Eudragit L100, la solubilisation se fait via la dissociation des fonctions carboxyliques. Ceci induit une acidification du milieu. Ainsi, plus la concentration en polymère sera élevée, plus la quantité d'ions H^+ libérée sera élevée. Il en résulte une acidification importante du milieu et le copolymère devient insoluble lorsque le pH devient inférieur à 6,5. Pour l'Eudragit E100, la solubilisation est réalisée via la protonation des fonctions amines. Il en résulte une basification du milieu. Cette dernière, fonction de la concentration en polymère, du pH initial du milieu et du temps rend insoluble l'Eudragit E100 lorsque le pH du milieu devient supérieur à 5,20.

Au vu des résultats obtenus en milieu HCl et NaOH, l'étude de solubilité des Eudragit E100 et L100 a été réalisée dans un second temps dans des milieux tampons. Nous avons donc procédé à des essais de solubilisation des deux copolymères à différentes concentrations dans des solutions tampons. Bien qu'ici également, les deux copolymères induisent une modification du pH des solutions tampons (acidification dans le cas L100 et basification dans le

cas E100), celle-ci est moins prononcée que précédemment. La modification de pH est d'autant moins perceptible que la concentration en tampon est élevée. Nous avons pu confirmer au travers de cette seconde étude de solubilisation les limites de solubilité vis-à-vis du pH, énoncées précédemment. Il ressort donc de cette étude que l'Eudragit E100 est soluble pour des valeurs de pH inférieures à 5,20 alors que l'Eudragit L100 est soluble pour des valeurs de pH supérieures à 6,5.

Pour ce qui est de la titration des groupes fonctionnels, la titration des groupements carboxyliques de l'Eudragit L100 a été réalisée par dosage à la soude sur des suspensions à différentes concentrations. Pour l'Eudragit E100, un dosage en retour a été nécessaire pour établir la concentration en groupements amines de ce copolymère. Ces dosages ont permis d'estimer le taux de groupements amines de l'Eudragit E100 à 4 mmol/g de copolymère (8,5 nmol/mol) et celui des fonctions carboxyliques de l'Eudragit L100 à 6 mmol/g de copolymère (4,8 nmol/mol).

L'étude des conditions de précipitation a pour but non seulement de confirmer une nouvelle fois les domaines de pH pour la précipitation des deux copolymères mais aussi de déterminer les conditions nécessaires à l'obtention de dispersions stables. La précipitation réalisée par acidification ou basification directe conduit à des particules polydisperses avec des tailles de particules de l'ordre de plusieurs dizaines de microns de façon générale. Le potentiel zêta des particules d'Eudragit L100 s'est révélé être inférieure à zéro. Ceci pourrait être lié à la présence de fonctions carboxylates résiduelles le long des chaînes de polymères d'autant plus que des mesures réalisées en milieu tampon ont permis d'observer des potentiels zêtas proches de zéro. Ces valeurs proches de zéro pourraient être liées à une protonation complète des fonctions carboxylates. Pour les particules d'Eudragit E100, elles ont également présenté un potentiel zêta inférieur à zéro pouvant s'expliquer par la forte présence d'ions OH^- , les mesures étant effectuées en milieu basique (milieu de précipitation). Le caractère cationique

des particules d'Eudragit E100 a cependant été révélé par des mesures effectuées sur des échantillons présentant un pH neutre. En effet, ces particules ont présenté un potentiel zêta de +24 mV, valeur probablement due à la présence de groupements amines cationiques le long des chaînes de polymère. Les images de microscopie sur les dispersions préparées en milieu tampon nous ont permis d'observer des particules d'Eudragit E100 et L100 de forme sphérique, polydisperses comme nous avons pu le voir par les différentes mesures effectuées en diffraction de lumière.

Nous avons pu observer comme cela est le cas pour la plupart des polymères, que la taille moyenne des particules augmente lorsque la concentration en polymère augmente. Dans le même sens, la distribution de taille de ces particules s'étend lorsque la concentration en polymère augmente. Pour terminer sur cette première étude expérimentale menée, nous avons observé que la concentration en sel n'avait pas d'influence significative sur les domaines de solubilité et de précipitation des copolymères étudiés. Nous avons été amenés à conclure que la précipitation des deux copolymères n'est pas induite par un écrantage de charges mais par un mécanisme d'annihilation de charges par protonation/déprotonation.

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pH-SENSITIVE METHACRYLIC ACID-METHYL METHACRYLATE COPOLYMER EUDRAGIT® L100 AND DIMETHYLAMINOETHYL METHACRYLATE, BUTYL METHACRYLATE AND METHYL METHACRYLATE TRI-COPOLYMER EUDRAGIT® E100

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Abstract :

Poly (methyl methacrylate) derivatives such as Eudragit are polymers largely used for drug encapsulation and in controlled oral drug delivery. With special focusing on those applications, solubilization and precipitation conditions of two pH-sensitive Eudragit polymers namely L100 and E100 were investigated via systematic studies. Effects of various physico-chemical parameters such as pH, polymer concentration, salinity, buffer concentration and incubation time on the solubilization and precipitation of these polymers were studied. In addition, pH titration of both polymers was reported. Considering both macroscopic and quantitative aspects such as the final mean particle size, size distribution, morphology and the zeta potential, it was established that the different pre-cited parameters could not be dissociated and exert a synergic action on the solubilization and precipitation of both polymers. In this study, the solubilization and the precipitation domains were for the first time clearly established by considering the above-mentioned parameters. Moreover, it was found that Eudragit L100 and E100 did not behave as classic polyelectrolytes since solubilization and precipitation domains were not affected by ionic strength. Titration curves revealed two equivalences that helped estimating carboxylic content of Eudragit L100 (6 mmol/g) and

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ammonium content of Eudragit E100 (4 mmol/g).

Keywords : Eudragit polymers, pH-sensitivity, solubilization, precipitation, dispersion.

3.1 Introduction

Nowadays, polymers are widely used in various domains such as painting, cosmetics, environmental analysis, in vitro biomedical diagnosis and in drug delivery. In therapy and theranostic applications, various processes [1] and numerous polymers [2] have been used for the encapsulation of active molecules. In this domain, polymers are mainly used because of their degradability, easy elimination by the body and good biocompatibility [3]. Moreover, these drug carriers are able to efficiently deliver therapeutic agents to target sites [4]. This is due to the polymeric properties which allow the preparation of nanoparticles with controlled size, size distribution, permeation, flexibility and solubility [5]. In order to improve their use, fundamental research has led to the development of a new class of smart carriers based on stimuli-responsive polymers [6]. These polymers can undergo several conformations as a function of the environmental conditions such as pH, temperature, solvent, ionic strength, light, magnetic or electrical fields [3, 7]. Due to their unique properties, materials prepared using these polymers are known as smart materials. Stimuli-responsive polymers are generally classified in two main categories depending on their response to external stimuli : (i) Physical stimuli, such as temperature, light, electrical or magnetic fields cause intermolecular interactions and (ii) chemical stimuli which change the molecular structure of the polymer by the addition of chemical agents or by changing the physicochemical properties of the used solvent such as pH and ionic strength for instance [8]. Moreover, polymers can be sensitive to more than one stimulus, which makes them dual-stimuli-responsive or multi-stimuli-responsive. These sensitive polymers are used in several applications such as drug delivery, membrane coating [7], as artificial organs, sensor materials [9], etc.

pH-Sensitive polymers are generally macromolecules containing potential ionizable groups or hydrolysable compounds. Then, by changing the pH of the medium, the degree of ionization, the solubility and the conformation of the polymers are affected [10]. This is due to the interaction between the solvent molecules and the polymer chains. For water soluble polymers, the solubilization is related to various physicochemical parameters of the medium. Therefore, the polymers may not be soluble or totally soluble in appropriate pH domain. Typically, the concerned polymers are water-soluble when charged compounds are induced and the degree of charged monomers is sufficient to induce affinity interaction with water molecules. Normally, such phenomenon is generally a reversible process. The most used and studied pH-sensitive polymer is poly acrylic acid (PAA) homopolymer and poly acrylic acid derivatives as largely reported [11]. Special attention has been dedicated to the swelling and deswelling ability as a function of pH and salinity rather than its precipitation. This synthetic polymer is easy to prepare using mainly classical radical polymerization process. Nevertheless, this polymer has not been explored to prepare pH-sensitive particles since as homopolymer it was found to be hard to precipitate without any chemical modification of its structure.

In the case of natural pH-sensitive polymers, chitosan has been studied in terms of chemical modification of its structure and pH precipitation as a function of both acetylation degree and pH of the medium [12, 13, 14]. This polymer has been largely studied and used in the encapsulation of numerous active molecules and special attention has been dedicated to cell transfection and gene therapy [15]. Beside the natural source of this biodegradable polymer, it is interesting to mention that its molecular weight and purity degree are hard to control from batch to batch due to the original source of the crude material [16].

Various non charged and synthetic polymers have been used in the encapsulation of active molecules, nanocrystals, oils, essential oils, proteins and nucleic acids for a wide range of ap-

plications not only in life sciences but also in environmental domains [17]. However, the use of pH-sensitive polymers to prepare pH-sensitive capsules or particles has not been widely reported as it can be evidenced from the few reported publications. This behavior may be attributed to few potential applications based on pH-sensitive environment [18].

The use of pH-sensitive particles in drug delivery has been stimulated by the possible influence of local pH of the tumor tissue to induce drug release [19, 20]. Then, various pH-sensitive carriers have been reported [21, 22, 23], but the literature is free from any deep characterization of the used polymers. In fact, polymethyl methacrylate derivatives have been used to encapsulate active molecules using double emulsion solvent diffusion [24], double emulsion solvent evaporation [1] and nanoprecipitation processes [25]. This last process has been largely studied and used to encapsulate hydrophobic active molecules [26, 27]. The most used polymethyl methacrylate polymers are named EUDRAGIT[®] [28]. Eudragit polymers have been used in nanoprecipitation process such as non-charged polymers soluble in polar organic solvents (ethanol, acetone dichloromethane) and charged polymers or ionizable polymers in water. Hence, the aim of this research work is to investigate the effect of different physicochemical parameters such as pH, salinity, polymer concentration, buffer concentration and incubation time on the solubility and precipitation of two oppositely charged poly methyl methacrylate derivatives named Eudragit L100 and Eudragit E100.

3.2 Materials and methods

3.2.1 Materials

Eudragit L100 (methacrylic acid-methyl methacrylate copolymer (1 :1)) powder (Mw=125000 g/mol) and Eudragit E100 (dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate tri-copolymer with a ratio of 2 :1 :1) pellets (Mw=47000 g/mol) were obtained from Evonik Röhm GmbH (Darmstadt, Germany)(Figure 3.1). Sodium hydroxide

was from Sigma Aldrich (Sweden) and hydrochloric acid (35%) was purchased from VWR Chemicals (France). Anhydrous disodium hydrogen phosphate (HNa_2PO_4) and sodium dihydrogen phosphate monohydrate ($\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$) from E. Merck (D-6100 Darmstadt, F.R. Germany) were used for the preparation of buffer solutions. Sodium chloride was obtained from Laurylab (Brindas, France).

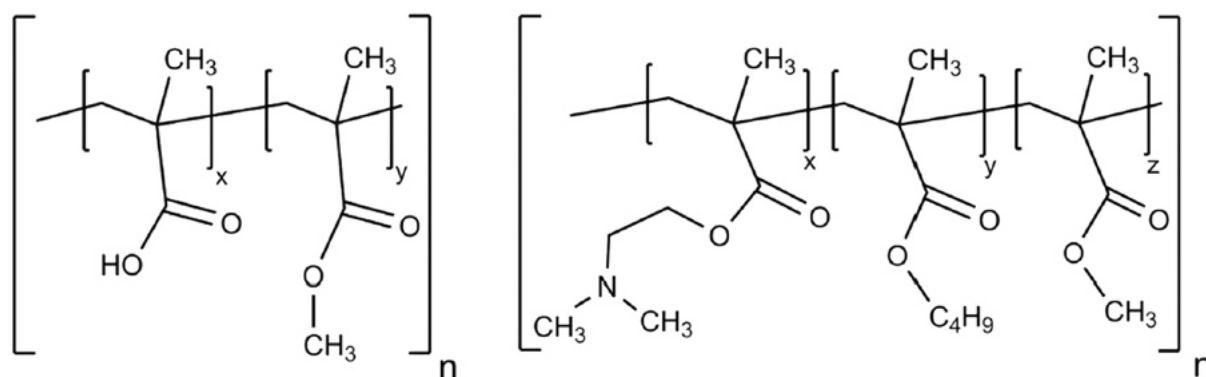


FIGURE 3.1 – Molecular structures of methacrylic acid - methyl methacrylate copolymer (1 :1) EUDRAGIT[®] L100 (left) and dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate tri-copolymer (2 :1 :1) EUDRAGIT[®] E100 (right) from Evonik Röhm GmbH (Germany).

3.2.2 Methods

Solubilization

Eudragit L100 powder was solubilized either in sodium hydroxide or in disodium hydrogen phosphate buffer solutions when Eudragit E100 pellets were solubilized either in hydrochloric acidic or in sodium dihydrogen phosphate buffer solutions. Solubilization experiments were conducted under continuous magnetic stirring. pH measurements were performed using a Mettler Toledo instrument LE420 (Mettler Toledo GmbH, Switzerland).

pH-titration of Eudragit L100 and E100

Eudragit L100 The pH titration was performed using five different concentrations (0.01, 0.05, 0.1, 0.5 and 1 wt.%) of Eudragit L100 dispersed in water. 10 mL of polymer suspension were titrated using NaOH solutions at different concentrations according to the equivalence point (from 1 M to 0.01 M). The titration was made under stirring, at room temperature and the pH was measured as a function of the NaOH added volume.

Eudragit E100 Back titration of Eudragit E100 pellets was performed by first dissolving the pellets in 1 M HCl solution. As for L100, five polymer concentrations were titrated. 10 mL of polymer solution were then dosed with NaOH solutions at different concentrations (from 1 M to 0.01 M). The titration was performed under continuous magnetic stirring and the pH was measured as a function of the NaOH added volume.

Precipitation

Eudragit L100 and E100 were first solubilized in appropriate pH conditions and then precipitated by changing the pH of the medium.

Particle size distribution

Hydrodynamic particle size and size distribution of the precipitated polymers were measured by dynamic light scattering (DLS) using a Zetasizer Nano ZS (Malvern Instruments, France) in the case of submicron particles and by light diffraction using a Mastersizer 3000 (Malvern Instruments, France) in the case of micrometric size. For light diffraction, the measurements were performed in deionized water and in 10^{-3} M sodium chloride solution for dynamic light scattering measurements.

Zeta potential measurement

Zeta potential deduced from electrophoretic mobility measurement of all obtained suspensions was measured using a Zetasizer Nano ZS (from Malvern Instruments, France) at a given pH, salinity and at room temperature. Each value is the average of more than 5 runs.

Particle morphology

The morphology of all prepared dispersions was observed using Transmission Electron Microscopy (TEM ; Philips CM120 electron microscope (CMEABG), University Claude Bernard Lyon 1). A drop of a diluted dispersion sample was deposited onto a carbon-coated copper grid and then allowed to dry at room temperature overnight before TEM imaging.

3.3 Results and discussion

The water solubility of the two Eudragit polymers has not been deeply analyzed in literature since all reported studies are mainly dedicated to the use of these polymers after solubilization in high acidic or basic mediums. In addition, to enhance the solubilization of the polymers, incubation at high temperature has also been used. However, if these polymers should be used in particles preparation, special attention should be focused on all parameters leading not only to their solubilization but also to their precipitation.

3.3.1 Solubility domains

The first step of this systematic study is to determine for each polymer the solubility pH domain as a function of the polymer amount, the incubation time and the initial pH of the medium. Four different initial pH were investigated for the solubilization of Eudragit L100 (pH=14, 13, 12 and 10) since it was known to be soluble in basic conditions. Inversely, Eudragit E100 solubilization study was realized in acidic conditions (pH= 0, 1, 2, and 3) [29].

Eudragit L100 solubilization in sodium hydroxide solutions results are presented in Figure 3.2. The studied parameters and their influence on the medium's pH and consequently on the solubilization of Eudragit L100 is shown. The grey bars on the 3D graphics refer to the solubilized samples whereas the others remain insoluble. Analysis of these results shows that the pH of the polymer solutions decreases as a function of time. This is attributed to the acidic property of Eudragit L100. Firstly, the polymer dissolution is faster at high basic pH and the dissolution decreases with the increase of polymer amount. For a given initial pH solution, the increase in the polymer amount induces a high decrease of the pH. Then, the change in the pH from basic to acidic reduces drastically the solubilization of the polymer. In brief, even if the initial solution pH is highly basic, the added polymer amount induces a shift in pH from basic to acidic leading to low and less polymer solubility.

Regarding Eudragit E100, a similar approach was used, and the obtained results are reported in Figure 3.3. This polymer is first solubilized in acidic HCl solution, but the total solubilization depends on the amount of used polymer and non-instantaneous solubilization was observed. The grey bars on the 3D graphics also refer to the solubilized samples whereas the others remain insoluble. When the medium initial pH is 3 for instance, no solubilization was observed even for low polymer concentration and after 24 hours of incubation. As it can be easily deduced from Figure 3.3, this polymer acts as a polybasic molecule since the increase of the polymer amount induces an increasing shift toward basic pH leading to less self-solubilization of the polymer.

Acrylic polymers such as Eudragit E100 and Eudragit L100 are known to dissolve upon respectively deprotonation and protonation of functional groups at specific pH values. Eudragit L100 dissolves in a basic medium at room temperature following its carboxylic group deprotonation whereas E100 solubility is related to its tertiary amine groups [30]. It is important to highlight that in addition to the initial pH of the medium, the solubility conditions of

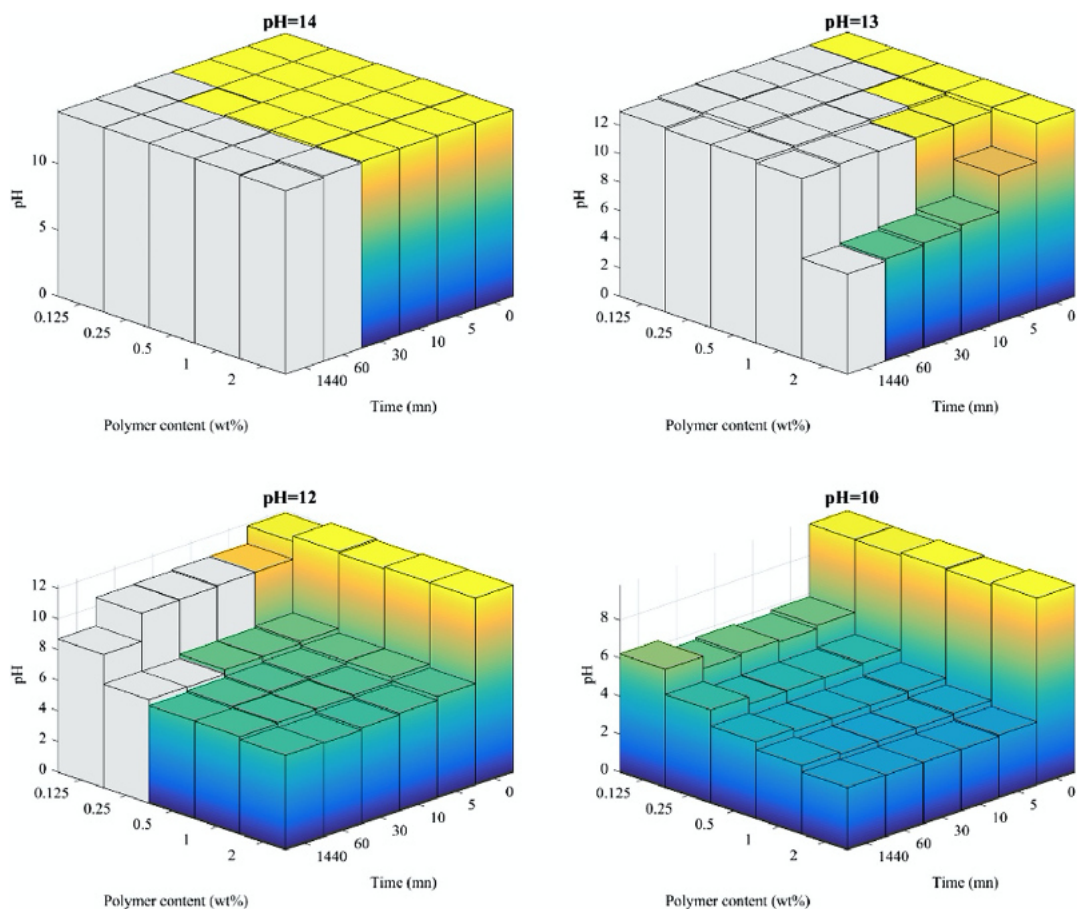


FIGURE 3.2 – Solubilization of Eudragit L100 in NaOH medium as a function of polymer amount and time. The grey bars refer to the solubilized samples whereas the other samples remain insoluble.

the two investigated polymers are closely related to the polymer content and its incubation time as shown in figures 3.2 and 3.3.

3.3.2 Solubilization in phosphate buffers

Since the used polymer amount affects the pH of the medium, the solubilization pH should be corrected by considering the shift induced by this parameter. Then, solubilization in phosphate buffers was investigated.

Various phosphate buffers were prepared, and different polymer amounts were used (see Table 3.1). As expected, the effect of the polymer on the initial pH is less marked compared

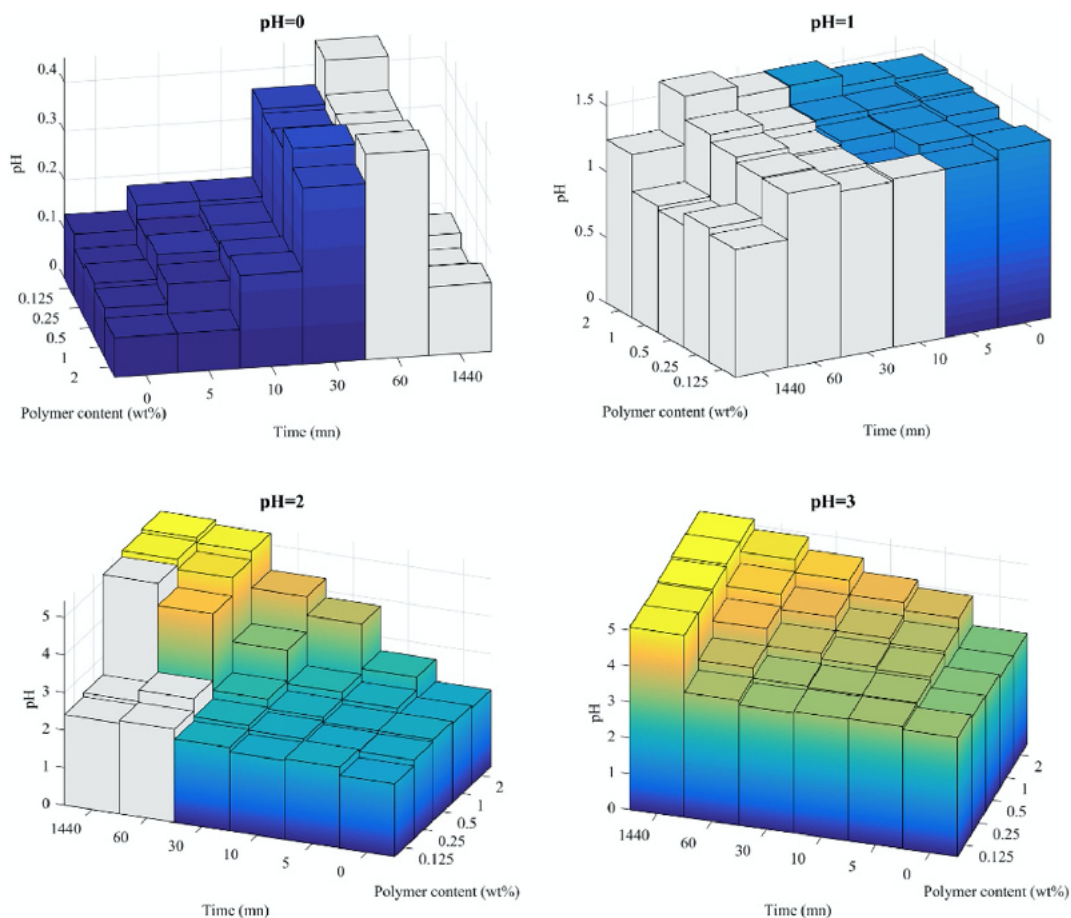


FIGURE 3.3 – Solubilization of Eudragit E100 in HCl medium as a function of polymer amount and time. The grey bars refer to the solubilized samples whereas the other samples remain insoluble.

to solubilization in HCl and NaOH solutions discussed previously. In addition, the higher is the buffer concentration, the easier and rapid is the solubilization of the polymer (for both polymers L100 and E100), whereas with low concentrated buffers, the initial pH was highly shifted to induce any solubilization.

This study on the solubilization in buffered solutions confirms that Eudragit L100 was soluble above $\text{pH}=6.50$ and Eudragit E100 up to $\text{pH}=5.20$. This behavior has not been reported in literature. The use of buffered solutions is important. Studying solubilization in HCl and NaOH solutions has no significant tangible meaning.

Buffer solution [HPO ₄ ²⁻ : H ₂ PO ₄ ⁻]	1 mM	10 mM	100 mM
Eudragit L100 wt.%			
70 : 30	5.86	6.47	6.67*
80 : 20	5.03	6.19	6.50*
90 : 10	6.03	6.29	7.14*
95 : 5	6.11	6.49	7.11*
Eudragit E100 wt.%			
30 : 70	6.70	6.80	6.83
20 : 80	6.59	6.68	6.74
10 : 90	6.44	6.53	5.20*
5 : 95	6.09	5.05	4.71*

TABLE 3.1 – pH measurements after 24h solubilization of either Eudragit L100 or E100 10 wt.% in phosphate buffer solutions at different volume ratios and concentrations. The pH marked with an asterisk refers to a total solubilization of the polymer.

3.3.3 Polymers titration

Due to the effect of polymer amount on the initial pH of HCl and NaOH solutions and also on low concentrated buffer solutions as above demonstrated, pH titration of each polymer was investigated.

Eudragit L100

Titration curves of Eudragit L100 obtained from direct pH-titration revealed two equivalences as shown in Figure 3.4. This is in agreement with the polyacid character of Eudragit L100 and it was observed irrespective of the polymer titrated amount. It is worth noticing that the polymer was not soluble until the pH of the first equivalence since the solutions remained turbid.

When the first equivalence was reached, the polymer was not totally solubilized, which means that the dissociated carboxylic groups amount was not sufficient to ensure a total solubilization of the polymer and the medium remained turbid. During the second equivalence, the solution became translucent ; the amount of dissociated carboxylic functions was enough

to ensure the solubilization of the polymer. This second equivalence was used to estimate the amount of carboxyl functions on the polymer, which was found to be equal to 6 mmol/g (ie, 4.8 nmol/mol).

Eudragit E100

pH titration of Eudragit E100 was also investigated, but before any discussion regarding this, it is worth mentioning that this polymer is under solid pellets compared to Eudragit L100 which is a powder. The pH-titration curve of Eudragit E100 revealed two equivalences for each studied polymer concentration as reported in Figure 3.4 for 0.5 wt.%. The first equivalence corresponds to NaOH titration, whereas the second equivalence corresponds to the titration of ammonium functions leading to the total precipitation of the polymer. This explains that the needed cationic ammonium amount to induce solubilization was reached and the titrated ammonium amount was found to be 4 mmol/g (i.e. 8.5 nmol/mol).

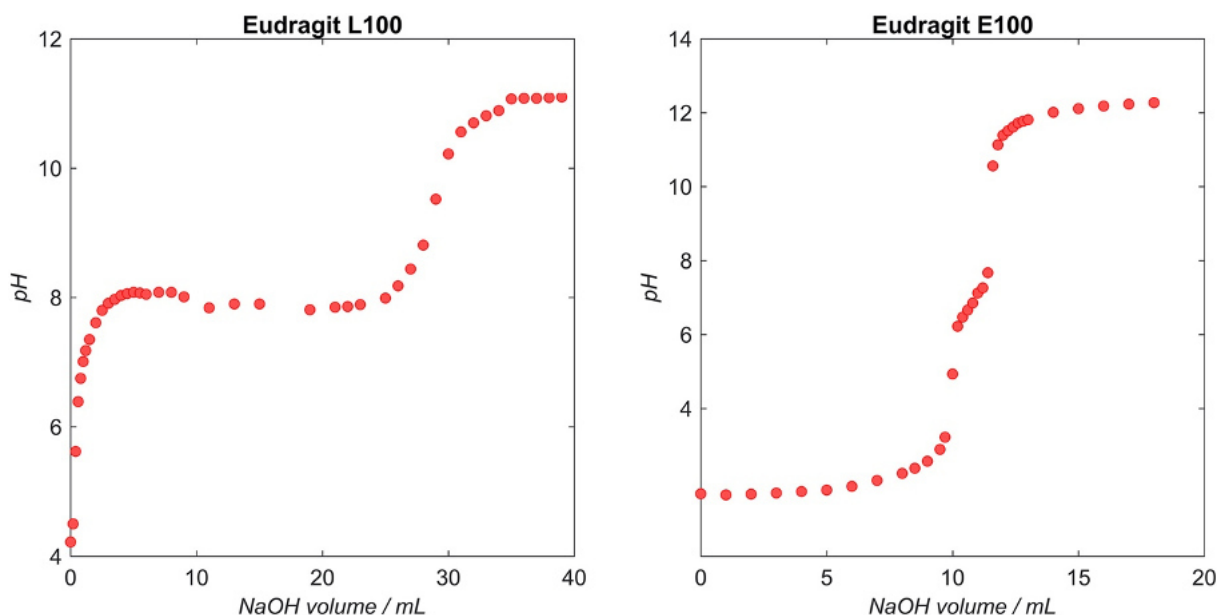


FIGURE 3.4 – pH titration of Eudragit L100 0.5 wt.% with NaOH 10^{-2} M solution (left) and Eudragit E100 0.5 wt.% solubilized in HCl 1 M with NaOH 10^{-1} M solution (right).

3.3.4 Polymers precipitation

After investigating the solubilization of both polymers as a function of initial pH, buffer pH and concentration, polymer amount and time, the precipitation study was conducted in order to point out the needed pH leading to polymer precipitation and to stable colloidal dispersions formation.

Eudragit L100

Firstly, Eudragit L100 was solubilized in high NaOH basic conditions (NaOH solution at pH=12, 0.25 wt.% of L100) and the precipitation was induced by adding the same volume of the polymer solution using HCl at various concentrations. Firstly, there was no precipitation of the polymer when COO^- terminations created by the solubilization step (and eventual OH^- ions in excess in the medium) were not neutralized by the addition of a sufficient HCl amount. Under the conditions of our experiments, for concentrations of hydrochloric acid solutions less than 10^{-2} M, there was no precipitation. Low HCl concentrations led to pH values out of the precipitation domain of L100 as reported earlier.

All final precipitated samples were turbid revealing the presence of objects and the measured zeta potential was found to be negative. This negative charge can be attributed to the presence of carboxylate groups on the formed particles.

In addition to zeta potential measurements, the hydrodynamic size of the obtained particles was measured by light scattering. Figure 3.5 shows the volume-based size distributions of the precipitated samples. Interestingly, all the obtained distributions were micrometric in size with a large size distribution. This can be attributed to the low colloidal stability of the formed particles. The lowest hydrodynamic mean size and narrowest size distribution were obtained with the smallest HCl concentration that has induced precipitation (10^{-2} M in the case of our experiments). The corresponding run led to a final pH of 2.9 and exhibits a high

zeta potential (-11 mV) with a better colloidal stability compared to other runs.

Eudragit E100

A similar study was conducted using Eudragit E100. Firstly, the polymer was solubilized in HCl solutions and then precipitated by adding a volume of NaOH solution identical to that of the Eudragit solution. Different NaOH concentrations were considered and the same observation as for Eudragit L100 was made. In fact, there was no precipitation of the polymer when ammonium ions (with eventual H^+ ions in excess in the medium) were not neutralized by the addition of a sufficient NaOH amount. There was no precipitation induced by NaOH concentrations below 10^{-2} M, the pH of the medium remains too acid and the polymer solution remains clear. The zeta potential of all obtained dispersions was found to be negative as expected since the measurements were performed at high basic pH. This negative zeta potential can be attributed to the condensation of excess OH^- ions on the particles surface. However, when the pH of the medium is close to pH=7 for instance, the zeta potential was found to be +24 mV revealing the cationic character of the particles surface due to the presence of cationic ammonium functions.

The hydrodynamic size and size distributions of all turbid dispersions were investigated, and the obtained results are reported in Figure 3.5.

For the lowest concentrated NaOH solution (10^{-2} M), the size distribution was found to be largely polydisperse. This can be attributed to the non-sufficiency of the initial NaOH solution concentration to induce instantaneous and total polymer precipitation. In fact, the reached pH after adding a 10^{-2} M NaOH solution is around 7.65 which is close to the solubility domain. However, when the concentration of NaOH was increased, the size distribution was reduced leading to narrowly size distributed particles.

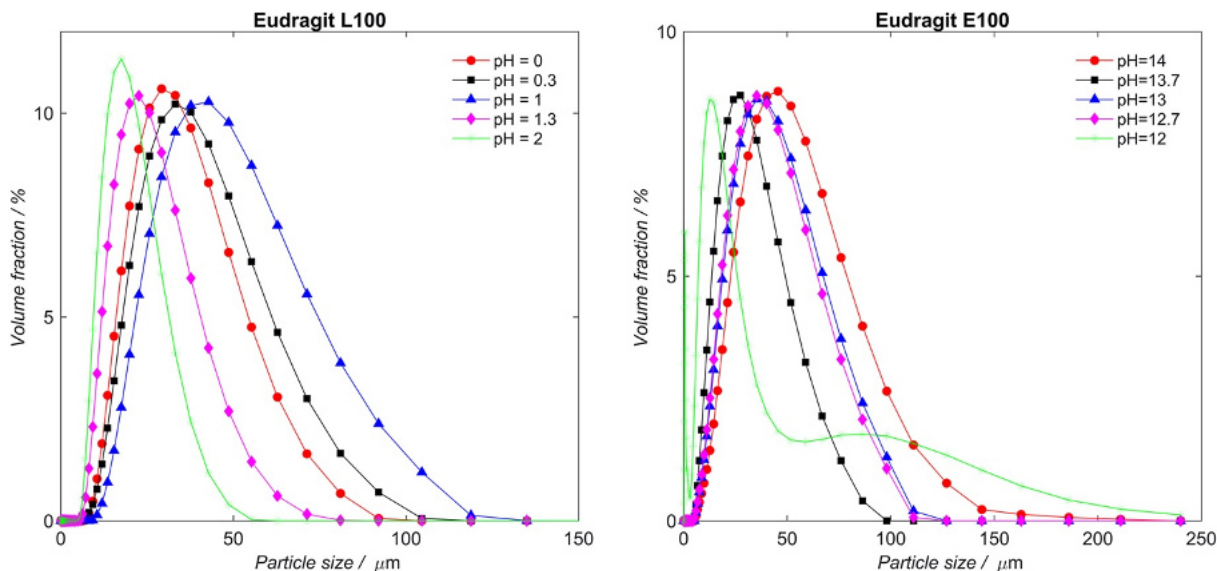


FIGURE 3.5 – Volume-based size distribution of precipitated Eudragit L100 (left) and Eudragit E100 (right) as a function of precipitating pH.

3.3.5 Effect of polymer amount on the precipitation process

As for any dispersion, the effect of material amount is of paramount importance since it may affect the nucleation step, the growing mechanism of the particles, the final size of the particles, the size distribution and by the way the colloidal stability of the obtained dispersion. Then, the effect of each polymer amount was individually investigated, and the obtained results are reported in this section.

Firstly, Eudragit L100 was solubilized in 8.10^{-2} M NaOH solution and Eudragit E100 in 8.10^{-2} M HCl solution for a given polymer amount. 10 mL of the NaOH solution in the case of Eudragit E100 and 10 mL of the HCl solution in the case of Eudragit L100 were then added to 10 mL of polymers solution at a given concentration and special attention is devoted to size and zeta potential analysis of the final dispersions.

Eudragit L100

Precipitation occurred irrespective of polymer amount and the final pH of the medium was found to be affected by the polymer concentration as above discussed. The obtained

particles are micrometric in size, widely distributed and negatively charged under the investigated pH. The observed negative zeta potential is attributed to the presence of carboxylic charges. The values are low, close to zero. This explains the non-colloidal stability of the formed dispersions and consequently, the particle size should be high compared to highly charged particles for the same polymer in more appropriate conditions as above reported.

As a general tendency regarding Eudragit L100, the hydrodynamic particles size and size distributions are lower when the polymer content in the medium is low (see Figure 3.6). These results are supported by that of Sheibat-Othman et al. [30] who demonstrated that increasing Eudragit L100 content leads to the formation of aggregates in a continuous process.

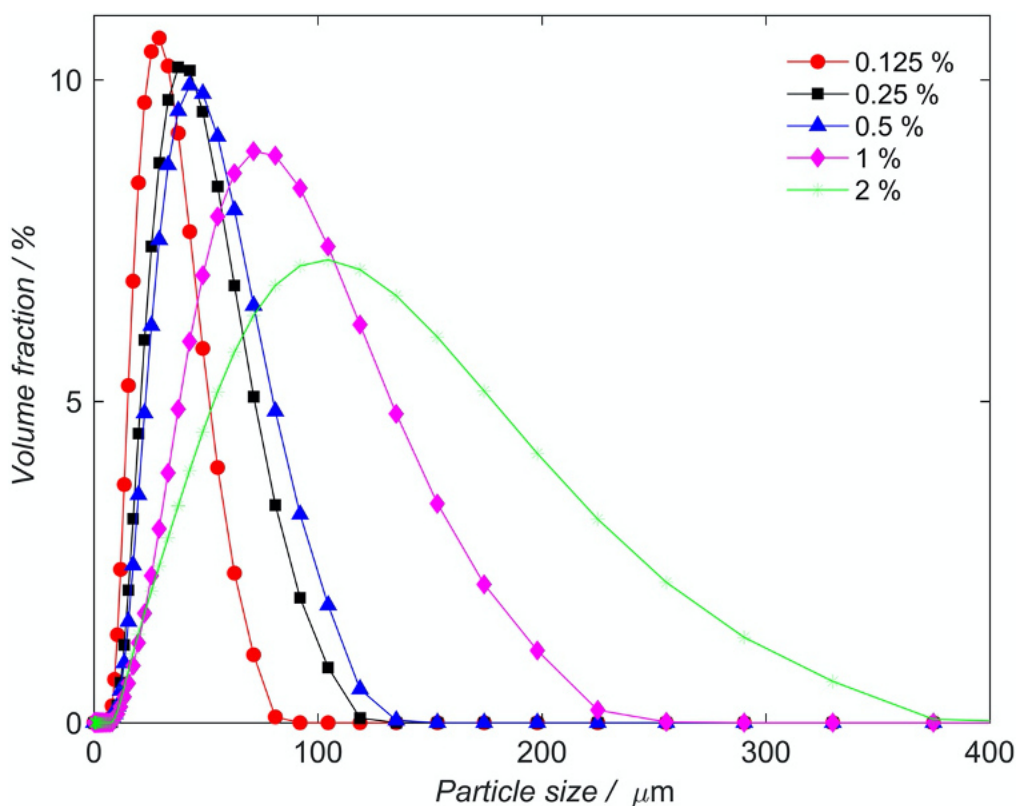


FIGURE 3.6 – Volume-based Eudragit L100 particle size distributions at different initial polymer concentrations.

Eudragit E100

Regarding Eudragit E100, the same methodology as for Eudragit L100 was used and the precipitation was not clearly evidenced. Only slightly turbid samples with 2 wt.% and 1 wt.% polymer content were observed. Results were in good agreement with the precipitation pH domain as reported in Figure 3.3. Indeed, the precipitation is only possible with the higher polymer concentrations (2 wt.% and 1 wt.%), leading to a final pH of the solutions respectively of 7.20 and 6.87. Samples with lower polymer content did not lead to any precipitation, which is explained by the acidic pH values of the final solution (Eudragit E100 is soluble up to 5.2). The excess of acid used for the solubilization was not neutralized and thus, the pH remains acidic.

3.3.6 Effect of buffer concentration

In order to control the precipitation pH and to reduce the effect of the polymers, a phosphate buffer (from 1 to 200 mM concentration) was used and added to the polymer solutions. Basically, 25 mL of phosphate buffer solution is added to 5 mL (20 wt.% polymer solution) and the precipitation was induced by adding 5 mL dropwise of NaOH or HCl 1 M. The obtained results are reported in Table 3.2 for Eudragit L100 and Eudragit E100 respectively.

As expected, the pH was not drastically shifted by the strong effect of the polymers. In all investigated phosphate buffer concentration domain, turbid systems were observed pointing out the precipitation of the used polymer. All obtained particles were micrometric in size and the mean particle size was found to be between 30 and 50 μm and the size distributions were large as observed by both diffraction light measurement (Figure 3.7) and TEM analysis (Figure 3.9). The zeta potential measured at the precipitation conditions was found to be negative for Eudragit E100. These negative values measured above pH=8 can be attributed to hydroxyl ions condensation around the formed particles, as above discussed.

Regarding Eudragit L100, the zeta potential measured in high acidic medium is found to be around zero. This is due to the total protonation of carboxylate function to carboxylic leading to almost non charged systems. Since the used polymers are pH-sensitive, it is totally impossible to investigate the effect of pH on the zeta potential. In fact, the particles will be totally solubilized in non-precipitation pH domain. As reported in Figure 3.8, TEM images show that all obtained dispersions are spherical polymer-based particles and highly polydisperse in agreement with diameters deduced from diffraction light analysis.

Buffer concentration (mM)	pH after precipitation	Aspect	Mean size (μm)	Zeta potential (mV)
Eudragit L100 20 wt.% with 1M HCl				
1	1.8	Turbid	46	-0.28
10	1.6	Turbid	43	-0.32
100	2.1	Turbid	50	-0.55
200	2.4	Turbid	46	-
Eudragit E100 20 wt.% with 1M NaOH				
1	11.6	Turbid	44	-14
10	11.4	Turbid	37	-12
100	10.0	Turbid	36	-8
200	8.3	Turbid	36	-

TABLE 3.2 – Precipitation of Eudragit L100 and Eudragit E100 20 wt.% with 1M HCl and 1M NaOH respectively.

3.3.7 Effect of ionic strength

The effect of ionic strength was investigated in order to point out if the presence of salt may affect the precipitation of the two polymers. The obtained results showed that whatever the concentration of salt (NaCl) in the buffer solution, the final pH of polymers precipitation was not affected as expected. As shown in Figure 3.9, the increase in ionic strength had no marked effect on the precipitation of both polymers and the same size and size distributions were obtained irrespective of salt concentration.

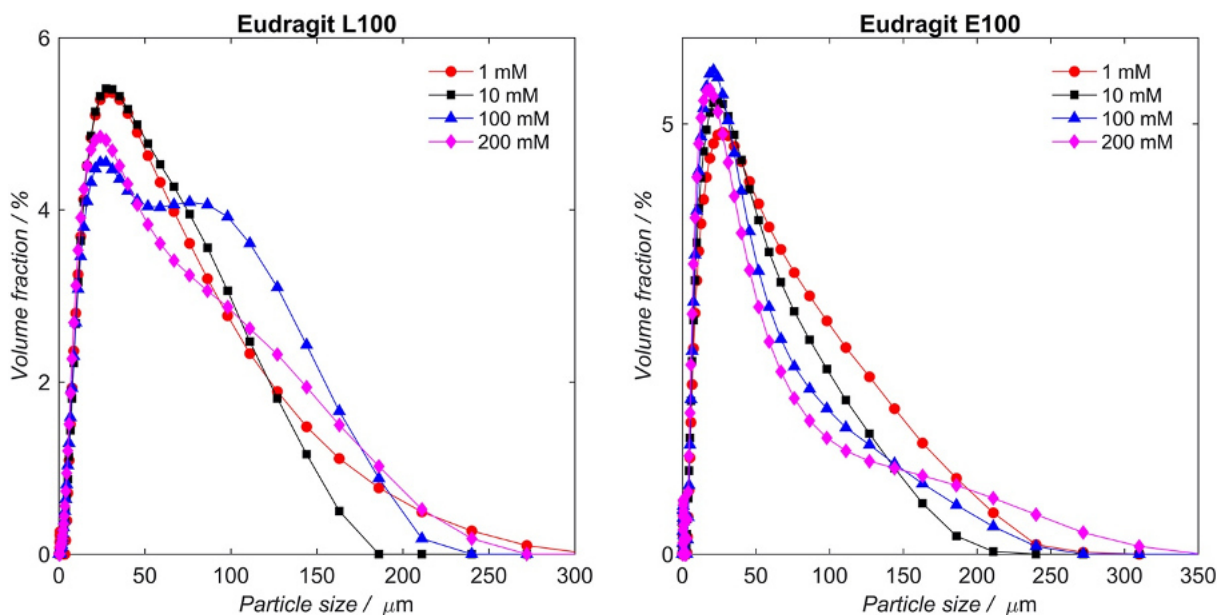


FIGURE 3.7 – Eudragit L100 (left) and Eudragit E100 (right) particle size distribution as a function of phosphate buffer concentration.

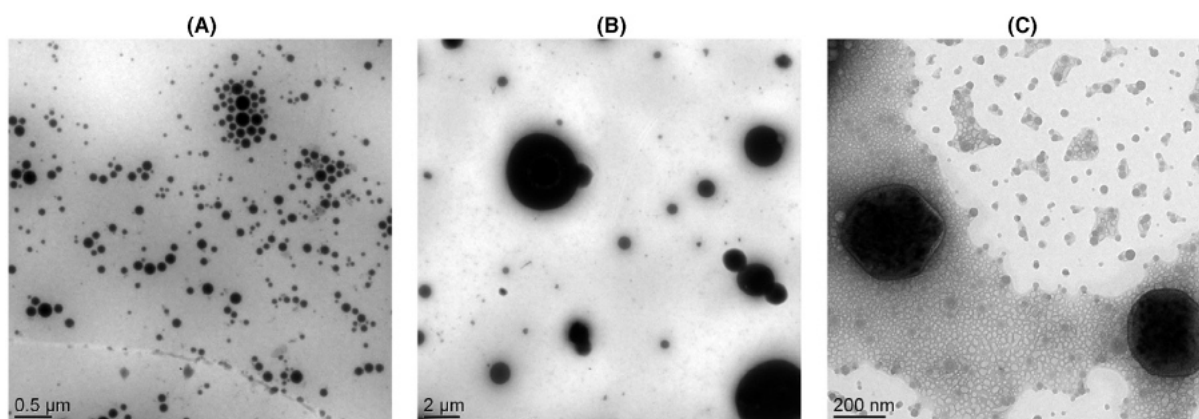


FIGURE 3.8 – Electronic microscopic pictures of 100 mM buffer Eudragit L100 (a), 10 mM buffer Eudragit E100 (b) and 200 mM buffer Eudragit E100 (c).

These results are in agreement with those obtained by Chern et al. who noticed that Eudragit L100 precipitation is not significantly affected by changes in the ionic strength of the medium [31]. Basically, the added amount of salt had no marked screening effect of polymer charges inducing polymer precipitation as generally observed in the case of classical polyelectrolytes [32]. Then, the driven force in precipitation process of these polymers is not charges screening, but charges annihilation-based mechanism via protonation or deprotonation.

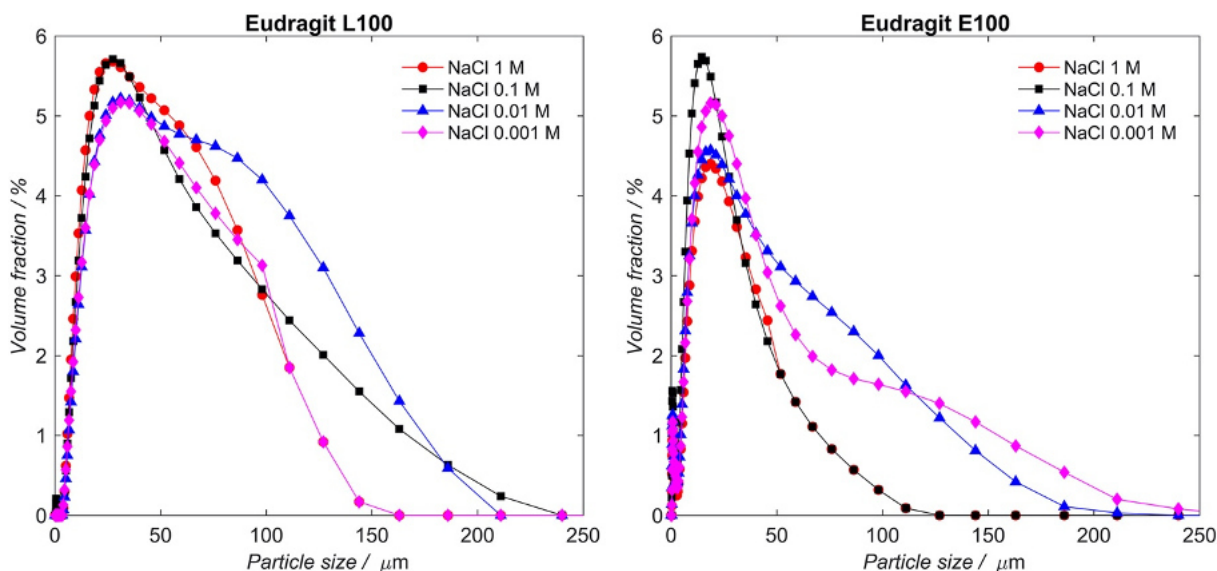


FIGURE 3.9 – Number-based particle size distribution of Eudragit L100 (left) and Eudragit E100 (right) as a function of NaCl concentration.

3.3.8 Co-precipitation of E100 and L100

As above discussed, both polymers can be precipitated by changing the pH only. Then, the mixture of both polymer solutions (prepared by solubilizing the polymers in either acidic or basic solutions) was investigated and special attention was dedicated to the colloidal characterization of the obtained dispersions as reported in Table 3.3.

Moustafine et al. studied the Eudragit L100 and E100 co-precipitation but in specific conditions especially in organic solvents at a fixed pH value of 6, pH at which both polymers are soluble and partially ionized [33]. Interaction between the two polymers in a molar ratio of 1 :1 led to the preparation of an interpolyelectrolyte, characterized in terms of turbidity, viscosity and chemical composition. Unfortunately, the study does not report neither the particle size nor the zeta potential.

In our experiments, we explore a larger range of pH conditions and the pH impact on the final suspensions in aqueous medium. All mixtures reported in Table 3.3 led to turbid dispersions which reflect the presence of particles. The zeta potential of all dispersions is

found to be negative at basic pH and positive at acidic pH. At basic pH, Eudragit E100 precipitated, leading to negative zeta potential, but this does not exclude the possible electrostatic attraction of Eudragit L100 with Eudragit E100 particles. It is interesting to notice that the negative zeta potential of the particles at pH above 4.5 is from polymer L100 and positive zeta potential is from E100.

Eudragit L100 (wt.%)	Eudragit E100 (wt.%)	Final pH	Mean size (nm)	Zeta potential (mV)
0.01 (pH=12.74)	0 (pH=1.31)	11.33	-	-35.5
0.01 (pH=12.74)	0.01 (pH=1.28)	2.39	-	+20.2
0.1 (pH=13.50)	0.01 (pH=1.28)	13.28	200 / 1258	-21.3
0.1 (pH=13.50)	0.05 (pH=1.30)	13.00	122/ 624	-20.6
0.1 (pH=13.50)	0.075 (pH=1.29)	12.69	299/4606	-19
0.1 (pH=13.50)	0.1 (pH=1.37)	1.22	175	+15.0
0.1 (pH=13.50)	0.125 (pH=1.46)	13.20	-	-20.6
0.1 (pH=13.50)	0.25 (pH=1.46)	12.97	-	-16.4

TABLE 3.3 – Equivalent volume addition of Eudragit L100 and E100.

3.4 Conclusion

Various physicochemical parameters affect the solubility and the precipitation of charged and non-charged polymers. In the case of pH-sensitive polymers such as methacrylic acid-methyl methacrylate copolymer (1 :1) and both charged poly (methyl methacrylate) (Eudragit L100 and Eudragit E100 respectively) which are largely used for encapsulation processes of active molecules, special attention has been dedicated to both solubility and precipitation domains. The correlation between solubility study in acidic (HCl)/basic (NaOH) solutions and phosphate buffers leads to the following : the polymer Eudragit L100 is soluble above pH=6.50 and the Eudragit E100 is soluble up to 5.20. It was shown that the polymer amount clearly affects the initial pH of the medium. Hence, the best way to control the solubility is to use an appropriate buffer medium. pH titration allows the determination of the amount of either carboxylic groups or ammonium groups for Eudragit L100 and E100 respectively.

It was found that Eudragit L100 contains around 4.8 nmol/mol of carboxylic groups and Eudragit E100 contains around 8.5 nmol/mol of ammonium groups.

After solubilization of each polymer in appropriate pH conditions, their precipitation was studied as a function of numerous parameters. Surprisingly, the precipitation of both polymers was found to be non-sensitive to the changes in the salinity of the medium as generally observed in the case of polyelectrolytes. This is probably due to the presence of water and polar methacrylate moieties. As for the solubilization study, the precipitation domain of each polymer was clearly established, and the obtained dispersions were characterized. The results show that the particle size is micrometric, with large size distributions and spherical shape as pointed out using TEM.

Finally, it can be concluded that for such pH-sensitive polymers (polymethyl methacrylate derivatives), the solubility and the precipitation domains are related to the initial pH, buffer concentration and polymer amount which are totally neglected in the state of the art.

Conflict of interest

The authors declare no conflict of interest.

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Chapitre 4

INFLUENCE DE POLYELECTROLYTES SECONDAIRES SUR LA PRECIPITATION DES EUDRAGIT E100 ET L100

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L'ajout d'additifs au cours de la cristallisation ou de la précipitation est connue pour entraîner des modifications au niveau des cristaux/particules produits. Ils peuvent en effet induire des modifications importantes au niveau de la taille des cristaux/particules, du faciès et aussi du polymorphisme [1, 2]. C'est dans ce sens qu'à la suite de notre première étude sur les conditions de solubilisation et de précipitation en solution des deux copolymères Eudragit E100 et L100, nous nous sommes intéressés dans un second temps à l'effet d'additifs sur la précipitation de ces deux copolymères [3]. Partant des résultats obtenus à l'issue de notre première étude, nous avons procédé à l'étude de l'influence de divers polyélectrolytes secondaires sur la précipitation des copolymères Eudragit E100 et L100 ainsi que sur les propriétés colloïdales des suspensions obtenues. Ont été étudiés d'une part des polymères non chargés (l'alcool polyvinylique, le dextran 40, le Pluronic F68) généralement utilisés comme stabilisant et d'autres parts des polyélectrolytes chargés (polyéthylèneimine, acide polyacrylique, amino-dextran) utilisés comme co-précipitant. De plus, la formation de polyplexes impliquant les Eudragit E100 et L100 et ces différents polyélectrolytes secondaires est abordée dans cette étude [4, 5, 6, 7]. Les dispersions obtenues suite à la précipitation des copolymères ont été caractérisées en termes de distribution de taille de particules, de potentiel zêta et de morphologie.

Les Eudragit E100 et L100 sont d'abord solubilisés respectivement dans de l'acide chlorhydrique et dans la soude pour des pH de solubilisation respectifs de 2,5 et 7 sur la base des résultats préalablement obtenus. Il est procédé ensuite à l'addition des polymères secondaires puis à la précipitation des polymères soit par acidification (cas de l'Eudragit L100) ou par basification (cas de l'Eudragit E100). Différentes concentrations en polymère secondaire ont été étudiées et le rapport massique polymère secondaire/Eudragit est noté "*w*". Comme pour l'étude précédente, la distribution de taille des particules a été obtenue par diffusion dynamique de la lumière via un Zetasizer Nano ZS (Malvern Instruments) pour les dispersions submicroniques et par diffraction de la lumière au Mastersizer 3000 (Malvern Instruments)

pour les dispersions micrométriques. Le potentiel zêta des particules préparées pour les différentes dispersions obtenues a été déduit de la mesure de la mobilité électrophorétique. Les mesures de potentiel zêta ont été réalisées pour une valeur de salinité et de pH donnée, les 2 copolymères étudiés étant sensibles au pH du milieu. La morphologie des particules préparées a été observée en microscopie électronique à balayage.

Il est important pour commencer de préciser qu'aucun des polymères secondaires n'a précipité seul dans les conditions de nos expériences. Sans polymère secondaire, des particules d'Eudragit L100 avec une distribution de taille autour de 20 μm ont été obtenues et un potentiel zêta de -11 mV (mesuré à pH=3 et $[\text{NaCl}]=1\text{mM}$). Ce potentiel zêta s'explique par la présence de groupements carboxylate résiduels sur la surface des particules. Dans le cas de l'Eudragit E100, des particules de taille moyenne autour de 40 μm ont été obtenues. Les mesures de potentiel zêta ont révélé des valeurs négatives liées à la condensation de groupements hydroxyles à la surface des particules lorsque les mesures sont réalisées en milieu basique. Proche d'un pH=7 et dans un milieu NaCl 1 mM, les particules d'Eudragit E100 ont présenté un potentiel zêta de +24 mV révélant le caractère cationique de leur surface lié à la présence de fonctions ammonium.

En présence de polymères non chargés (le polysaccharide dextran T-40, l'alcool polyvinylique, le Pluronic F68), aucun effet significatif n'a été observé sur la distribution de taille des particules d'Eudragit E100. Des particules de taille moyenne allant de 40-50 μm ont été obtenues. Ces résultats s'expliquent par le caractère non chargé de ces polymères secondaires qui ne présentent aucune interaction avec les copolymères étudiés. Aussi, aucune modification significative du potentiel zêta n'a été observée. Les particules ont présenté des potentiels zêta autour de -20 mV pour les différents polymères non chargés indépendamment des concentrations étudiées. Les deux copolymères étudiés étant sensibles au pH du milieu, nous n'avons donc pas procédé à une mesure du potentiel zêta en fonction du pH. L'acide polyacrylique,

chargé négativement n'a également montré aucune influence significative sur les particules d'Eudragit à faible concentration. Nous avons pu observer pour un ratio $w=1,33$ que l'acide polyacrylique induit une basification du milieu entraînant la précipitation de l'Eudragit E100. Des particules de taille moyenne (d_{50}) autour de $40 \mu\text{m}$ ont là également été obtenues avec un potentiel zêta mesuré à pH neutre de $-46,4 \text{ mV}$. Ceci s'explique par le fait que l'acide polyacrylique est chargé négativement. Cette précipitation suite à l'addition du polyélectrolyte secondaire a également été observée dans le cas du polyéthylèneimine chargé positivement avec des particules de taille moyenne (d_{50}) autour de $30 \mu\text{m}$ et un potentiel zêta proche de zéro mesuré à $\text{pH}=8$. Pour finir sur les particules d'Eudragit E100, le polyéthylèneimine et l'amino-dextran, tous deux chargés positivement n'ont présenté aucun effet aussi bien sur la distribution de taille des particules que sur le potentiel zêta des particules. Ceci s'explique par les forces répulsives liées au fait que ces deux polyélectrolytes tout comme l'Eudragit E100 présentent en solution les mêmes charges.

S'agissant des particules d'Eudragit L100, le dextran T-40 et l'acide polyacrylique n'ont présenté aucune influence significative sur les particules obtenues. Cependant, l'acide polyacrylique à un ratio $w= 1,33$ semble empêcher la précipitation de l'Eudragit L100 en milieu acide. L'alcool polyvinylique et le Pluronic F68 de leur côté ont entraîné une augmentation de la taille moyenne des particules. En effet, en présence de ces deux polymères secondaires, la taille moyenne des particules est passée de 20 à $60 \mu\text{m}$ pour un ratio w de 0 à $1,33$. Aussi le potentiel zêta de ces particules s'est révélé proche de zéro lorsque la concentration en alcool polyvinylique ou en Pluronic F68 est augmentée. Ceci est lié à la réduction de la charge de surface au niveau de la surface des particules due à la présence de ces polymères non chargés (effet d'écrantage des charges de surface). L'augmentation de la taille moyenne des particules et l'étalement des distributions de taille quant à elles peuvent s'expliquer par une agrégation induite par un phénomène de déplétion à l'étape de nucléation. Cette augmentation de taille des particules a également été constatée dans le cas de l'amino-dextran. Si à faible

concentration ce dernier n'a présenté aucune influence, nous avons obtenu à une concentration correspondant à un ratio $w=1,33$ des particules de taille moyenne autour de $375 \mu\text{m}$ avec un potentiel zêta de $+14 \text{ mV}$ qui s'explique par l'incorporation de l' amino-dextran qui est un polyélectrolyte chargé positivement dans la structure des particules préparées. L'influence la plus significative a été observée pour l'Eudragit L100 et induite par le polyéthylèneimine. En effet, en présence de ce polyélectrolyte, des particules d'Eudragit L100 sphériques avec une distribution de taille resserrée autour de 200 nm ont été obtenues pour des rapports w allant de $0,67$ à $1,33$ dans les conditions de notre étude. Des suspensions stables ont ainsi pu être obtenues avec des particules présentant un potentiel Zêta de $+45 \text{ mV}$. Ce potentiel zêta positif découle de la présence probable du polyéthylèneimine à la surface des particules et s'est avéré suffisant pour prévenir l'agrégation et assurer une bonne stabilité colloïdale. Aussi, le pH final des suspensions se situant dans le domaine de solubilité de l'Eudragit L100 associé au fait que dans ces conditions le polyéthylèneimine seul ne précipite pas laissent suggérer la formation dans les conditions de notre étude d'un complexe polyélectrolytique ou polyplexe associant l'Eudragit L100 et le polyéthylèneimine comparables à ceux élaborés par Pei Li et al. par copolymérisation par greffage pour le transport de matériel génétique [8, 9, 10].

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EFFECT OF SECONDARY POLYMER ON SELF-PRECIPIATION OF pH-SENSITIVE POLYMETHYLMETHACRYLATE DERIVATIVES EUDRAGIT E100 AND EUDRAGIT L100

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Abstract :

Interpolyelectrolyte complexes or polyplexes can be seen as interesting alternatives in the purpose of active ingredients encapsulation. Working on polymethylmethacrylate derivatives with special focus on controlled oral drug delivery, the influence of charged polyelectrolytes (polyacrylic acid, polyethylenimine, amino-dextran) and non-charged ones (polyvinyl alcohol, dextran 40, Pluronic F68) has been investigated on the precipitation of two pH-sensitive Eudragit polymers namely L100 and E100. Moreover, the possibility of preparing polyplexes involving the two polymethylmethacrylate derivatives with different charged and non-charged secondary polyelectrolytes has been studied. The obtained dispersions have been characterized in terms of mean particle size, size distribution, zeta potential and morphology.

Direct precipitation of Eudragit L100 by medium acidification in a batch process and in presence of polyethylenimine allowed the production of particles with a narrow size distribution. The mean size was around 200 nm. In this case, the zeta potential was found to be +45 mV at pH=7 in 1 mM aqueous NaCl solution and the produced suspension was stable in time since no aggregation and then no sedimentation has been observed. A precipitation pH of 8.16 allows us to suggest the preparation of a polyplex based on Eudragit L100 and polyethylenimine. In contrary, polyvinyl alcohol has shown ability to induce an increase in

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particle mean size whereas other polyelectrolytes showed no significant effect.

Moreover, it was observed that polyethylenimine and polyacrylic acid solutions were able to directly induce Eudragit E100 precipitation whereas amino-dextran and non-charged polyelectrolytes showed no effect on its precipitation and on particle size distribution.

Keywords : pH-sensitive polymers, dispersion, precipitation, self-precipitation, polyplex.

4.1 Introduction

Several polymers are nowadays used for the encapsulation of active molecules. This process covers a broad range of applications such as pharmaceutical, food, cosmetic, and textile industries. Among the commonly used coating materials, biodegradable polymers such as polysaccharides (starch, chitosan), proteins (gelatin, bovine serum albumin), polyesters (polylactide (PLA), polylactide-co-glycolide (PLGA) and polycaprolactone (PCL)), and polyether (polyethylene glycol (PEG)) are explored in the literature [1]. Moreover, non-biodegradable stimuli-responsive polymers are largely studied especially the polymethylmethacrylate derivatives [2].

In the pharmaceutical industry, drug encapsulation plays a major role since it increases the bioavailability of drugs [1]. Moreover, this process prevents the active ingredients from degradation and enhances the control and the drug release into specific sites. This is the case for pH-sensitive polymers which are used as drug carriers to prevent the enzymes and gastric fluids action or to reduce the gastrointestinal irritation caused by nonsteroidal anti-inflammatory drugs for example [3, 4].

Polymethylmethacrylate (PMMA) polymers (Eudragit[®]) are employed as drug delivery

systems targeting different specific organs such as stomach, duodenum and colon [5], epithelial cells and their membranes [6], skin surface and hair follicles [7, 8].

In a classical encapsulation process, the active molecules are entrapped in a single polymer matrix. However, polymers combination may be considered in order to confer specific and highly rated properties to the new coating materials that can allow the target of specific sites and sustainable release as well [9, 10]. In the literature, precipitates are obtained by mixing cationic and anionic polymers in aqueous solutions through strong and reversible electrostatic bonds and known as interpolyelectrolyte complexes (IPEC). It is known that the stoichiometry of both components in binary IPEC and the properties of final IPEC depend not only on the nature of the polymers (chemical composition, molecular weight, stereochemistry, charge densities) and their concentration but also on preparation conditions such as the mixing ratio, the order of polymers introduction, the pH of the medium and the ionic strength [9, 11, 12, 13].

The possibility of preparing interesting IPEC involving Eudragit polymers using different cationic and anionic grades have been largely studied; indeed, in vitro experiments highlighted their potential to be used in controlled drug delivery systems [14]. For example, the release of ibuprofen studied as a model drug was significantly delayed for tablets made with IPEC (Eudragit EPO and Eudragit L100-55) as compared with individual copolymers [15]. Moustafine et al. recently reported a novel system composed of two oppositely charged (meth)acrylate copolymers, Eudragit EPO and Eudragit S100, loaded with indomethacin. The use of the resulting IPEC slowed down the release process which makes the system suitable for colon-specific delivery [16].

Moreover, IPEC combining Eudragit polymers with other polyelectrolytes were also explored. Nanoparticles with a methacrylate core and a polyethylenimine shell prepared via

graft copolymerization have been synthesized and employed for gene delivery with a higher transfection efficiency and lower toxicity compared to polyethylenimine alone [17, 18]. Polymethylmethacrylate Eudragit E100 in combination with PLGA or PLA using a cationic surfactant (cetyltrimethylammonium bromide, CTAB) have been reported with higher transfection efficiency compared to PLA/CTAB and PLGA/CTAB nanoparticles [19].

Alongside pH-sensitive polymers and enzymatic degradable polymers, polysaccharides (biodegradable, non-toxic and easily available) are substrates for colonic bacteria enzymes. They can be exploited in coating and in colon drug delivery [20], this was the case for dextran (or dextran esters) polymers [21, 22].

Moustafine et al. combined chitosan with Eudragit L100 or Eudragit L100-55 as IPEC and showed a slower release of model drugs such as ibuprofen and diclofenac sodium [23, 24]. The delay was controllable by changing the molecular weight of chitosan in the complexes' composition. Li et al. prepared insulin-loaded nanoparticles with chitosan and Eudragit L100-55 complexes [25]. This system was found to be attractive for the entrapment of hydrophilic polypeptides specifically for oral delivery.

Interpolyelectrolytes involving Eudragit polymers with other polyelectrolytes of polysaccharide group such as sodium alginate have been reported in literature. Moustafine et al. worked on the synthesis of IPEC based on sodium alginate and Eudragit E100 [26] or Eudragit EPO [27]. With Eudragit EPO, the release of diclofenac sodium, used as a model system for colonic drug delivery, was significantly delayed whatever the composition of the polyplex. Sodium alginate and Eudragit E interpolyelectrolyte complex was investigated by Sepúlveda-Rivas et al. who showed its potential as an effective and viable nanocarrier throughout experiments realized with lysozyme enzyme as model drug [28]. They particularly highlighted the impact of variables such as the total charge (sum of positive and negative

charges) and the charge ratio (defined as the quotient between positive charges and negative charges) on nanoparticle physicochemical properties. By handling these two parameters, it was possible to control the size and the surface properties of the resulting lysozyme-loaded particles. Another example of polysaccharide used in IPEC synthesis is pectin which forms pectin–Eudragit complexes involving Eudragit RL and Eudragit RS. The capability of pectin–Eudragit RL complex to prevent the release of incorporated drugs has been demonstrated [29, 30].

Arango-Ruiz et al. used combination of two encapsulating polymers during the encapsulation process of curcumin using a supercritical antisolvent technology [31]. They found out that a mixture of Eudragit L100 and Pluronic F127 in presence of poly oxyethylene sorbitan monolaurate (Tween 20) as surfactant leads to spherical micrometric and monodisperse particles. However, any influence of Pluronic F127 on the particle size or shape have been highlighted or discussed even if it was clearly established that the final particles were made of encapsulated dry curcumin extract, Eudragit L100 and Pluronic F127.

Another approach in the synthesis of nanocarriers is the use of polyelectrolyte as emulsifier in the control of the physicochemical properties of drug delivery systems targeting specific sites. Emulsifiers are used to stabilize the formed particles and prevent them from aggregation. Thus, polyvinyl alcohol (PVA) has been used as an emulsifier in the batch precipitation process of Eudragit E100 and Eudragit L100 [32]. No clear effect has been noticed on the particle size at the tested concentrations. In contrast, Seremeta et al. found that Eudragit RS 100 plays the role of surfactant stabilizing polycaprolactone particles and promotes the generation of smaller particles when these two polymers are combined in the preparation of antiretroviral efavirenz-loaded particles by nanoprecipitation method [33].

The aim of the present research work is to study the influence of a secondary polymer

on the direct precipitation of two pH-sensitive methacrylic acid-methyl methacrylate copolymer Eudragit L100 and dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate tri-copolymer known as Eudragit E100. Due to their pH-sensitivity, their direct precipitation occurs by a simple acidification or basification of the medium [34] and the properties of the obtained dispersions such as the final mean particle size, size distribution, zeta potential and particle morphology are reported. The influence of different non-charged polyelectrolytes (polyvinyl alcohol, dextran 40, Pluronic F68) and charged polyelectrolytes (polyacrylic acid, polyethylenimine, amino-dextran) on the particles' formation and the colloidal properties of the dispersions is presented and discussed.

4.2 Materials and methods

4.2.1 Materials

Eudragit L100 (methacrylic acid-methyl methacrylate copolymer (1 :1)) powder ($M_w=125000$ g/mol) and Eudragit E100 (dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate tri-copolymer with a ratio of 2 :1 :1) pellets ($M_w=47000$ g/mol) were obtained from Evonik Röhm GmbH (Darmstadt, Germany). Sodium hydroxide was purchased from Sigma Aldrich (Sweden) and hydrochloric acid (35%) from VWR Chemicals (France). Sodium chloride was obtained from Laurylab (Brindas, France). Branched polyethylenimine (PEI, $M_w=25000$ g/mol, $M_n\sim 10000$) was purchased from Aldrich Chemistry (Germany), polyvinyl alcohol ($M_w=200000$ g/mol) from Merck KGaA (Darmstadt, Germany) and polyacrylic acid 40% wt. ($M_w=30000$ g/mol) from Aldrich Chemical Company (Milwaukee, USA). Dextran 40 ($M_w=40000$ g/mol) was a product of AppliChem GmbH (Darmstadt, Germany) and Pluronic F68 was purchased from Molekula Group (Shaftesbury, Dorset, Great Britain). Amino-dextran was prepared according to Mouaziz et al. [35] and using hexamethylenediamine from Merck (Germany) and Dextran-T40 from Amersham Biosciences (Germany)(Table 4.1).

Eudragit L100	
Eudragit E100	
Dextran T-40	
Polyacrylic acid	
Polyvinyl alcohol	
Pluronic F68	
Polyethylenimine	
Amino-dextran	

TABLE 4.1 – Molecular structures of Eudragit L100, E100 and studied secondary polymers.

4.2.2 Methods

Precipitation process

Eudragit[®] L100 and E100 solutions at a concentration of 2,5 g.L⁻¹ were prepared by solubilizing Eudragit L100 powder and E100 pellets in sodium hydroxide and hydrochloric acid 10⁻² M solutions respectively. The solubilized Eudragit L100 and E100 were precipitated by the addition of either hydrochloric acid solution (in the case of L100) or NaOH solution (for E100). For this purpose, in a typical experiment of Eudragit L100 precipitation, 40 mL of hydrochloric acid solution 10⁻² M were instantaneously mixed with 40 mL of a mixture composed of 30 mL of Eudragit L100 solution and 10 mL of a solution of polyelectrolyte. For Eudragit E100, the same procedure as for Eudragit L100 was used with precipitation occurring by addition of sodium hydroxide 10⁻² M solution instead of hydrochloric acid solution. The resulting suspensions were maintained under stirring and were further characterized in terms of final mean particle size, size distribution, zeta potential and particle morphology.

Characterization

Particle Size Distribution (PSD) The hydrodynamic mean particle size and size distribution of the precipitated polymers were determined by Dynamic Light Scattering (DLS) using a Zetasizer Nano ZS (Malvern Instruments, France) in the case of submicron particles and by light diffraction using a Mastersizer 3000 (Malvern Instruments, France) in the case of micrometric sized particles. For diffraction, the measurements were performed in deionized water and DLS measurements were performed in 10⁻³ M sodium chloride deionized water solution.

Zeta potential measurement The zeta potential was deduced from the electrophoretic mobility measurements of all obtained suspensions and was measured using a Zetasizer Nano ZS (from Malvern Instruments, France) at a given pH, salinity and at room temperature. Each value is the average of more than 5 runs. Zeta potential measurements were realized at

resultant suspensions pH if any other information provided.

Particle morphology Scanning Electron Microscopy (SEM, FEI QUANTA 250 FEG) was used to determine the surface morphology of the particles. A drop of diluted sample was deposited on a flat steel holder and dried at room temperature and then analyzed under an accelerating voltage of 10 kV.

4.3 Results and discussion

The effect of non-charged polymers (Dextran-T40, polyvinyl alcohol and Pluronic F68), negatively charged polyacrylic acid and positively charged polyethylenimine and amino-dextran on Eudragit L100 and Eudragit E100 precipitation are investigated. Different concentrations of the studied polyelectrolytes are tested. The mass ratio polyelectrolyte/Eudragit polymer is identified as “ w ”. Effects on final mean particle size, size distribution, zeta potential and on the particle morphology of the obtained dispersions are discussed. None of the studied second polymer precipitates alone under the investigated experimental conditions.

4.3.1 Precipitation of Eudragit L100 and Eudragit E100

Eudragit L100 and E100 were first solubilized in appropriate pH conditions and then precipitated by changing the pH of the medium in the presence of the second polymer mentioned before. Solubilization conditions were set up in order to have Eudragit solutions with low viscosity since the polymer amount was shown to have an impact on the elaborated particles size. In a previous study, we established the Eudragit L100 and E100 solubilization and precipitation domains and showed that they precipitated exactly under pH values of 6.5 and 5.2 respectively by direct acidification or basification leading to milky-like dispersions with large size distributions. The obtained suspensions with Eudragit L100 exhibited negative zeta potential. This negative value may be attributed to the presence of carboxylate groups on the formed particles. For Eudragit E100, the zeta potential of all obtained dispersions was

found to be negative. This negative zeta potential may be attributed to the condensation of excess OH^- ions on the particles surface since the measurements were realized in basic conditions. However, when the pH of the medium is close to $\text{pH}=7$, for instance, the zeta potential was found to be $+24$ mV revealing the cationic character of the particles surface due to the presence of cationic ammonium functions [34].

4.3.2 Influence of Polysacharrides (Dextran-T40)

The different concentrations of Dextran-T40 tested showed no evident influence on the particle size distribution neither on Eudragit L100 precipitated particles, nor on Eudragit E100 ones. The final mean size of Eudragit L100 particles was around $10 \mu\text{m}$ for a weight ratio w of 0.0133, whereas the final mean particle size for other dextran concentrations was established between 15 and $20 \mu\text{m}$. Meanwhile, the final mean size obtained for Eudragit E100 particles was around $40 \mu\text{m}$ whatever the ratio w . The zeta potential of the different samples obtained from these two series of experiments remains the same regardless of the amount of Dextran-T40 (around -11 mV and -22 mV respectively for L100 and E100 samples).

The effect of such non-charged polymer on the final particles size and zeta potential is totally negligible. The used dextran T-40 is a non-charged polymer and has no amphiphilic property. In addition, this polymer has no possible acidic or basic compound. Consequently, the inert polymer has no drastic effect on particle size, size distribution and surface charge density (i.e. zeta potential) of pH-sensitive Eudragit L100 and E100 polymers.

4.3.3 Influence of polyacrylic acid

The effect of polyacrylic acid, a negatively charged polyelectrolyte, on the two Eudragit polymers was investigated. Polyacrylic acid does not appear to have any significant influence on the particle size distribution of both Eudragit L100 and E100 whatever its concentration.

For the value $w=1.33$ (%wt.) corresponding to the largest quantity of polyacrylic acid tested, there was no precipitation of Eudragit L100. Thus, a high polyacrylic acid amount seems to avoid Eudragit L100 precipitation. In contrary, for the same value of w , Eudragit E100 precipitated directly with no need to add sodium hydroxide solution to the formulation. The final pH of the suspension was 6.76 which corresponds to the precipitation domain of Eudragit E100 [34]. This precipitation seems to be due to the medium basification induced by the polyacrylic acid solution. Resulting particles exhibit a highly negative zeta potential (-46.4 mV) measured at pH=7.

It is worth noting that the amount of polyacrylic acid does not have any significant impact on the zeta potential of the precipitated Eudragit L100 particles (-12 mV for w values of 0,133 and 0,0133 %wt.). However, for Eudragit E100 dispersions, an increase of the zeta potential in absolute value is noticed with the increase of the amount of polyacrylic acid (from -24 mV to -46.4 mV for w values respectively from 0 to 1.33 %wt.). This is explained by the increase of surface charges density by the presence of the charged polymer.

4.3.4 Influence of polyvinyl alcohol

Figure 4.1 shows the particle size distribution of the precipitated Eudragit under different concentrations of PVA. It clearly appears that the presence of polyvinyl alcohol affects the mean size of Eudragit L100 particles. Thus, the mean size of Eudragit L100 particles increases with the amount of PVA. For the highest amount of PVA, the mean size is around $60 \mu\text{m}$, whereas without PVA this mean size is around $20 \mu\text{m}$. These results are in concordance with observations realized by Sheibat-Othman et al. [32] who noticed that smallest Eudragit L100 particles are obtained with smallest PVA amount used as emulsifier.

By increasing the amount of PVA, it was found that the zeta potential of the particles decreases in absolute value from -11 to -1.6 mV (for w values from 0.0133 to 1.33 %wt.).

The zeta potential measured for the highest concentration of PVA is close to zero, which is related to the reduction of surface charges by the presence of the non-charged polymer (i.e screening effect). Indeed, PVA is a non-charged polymer that seems to not interact with Eudragit L100. Therefore, the increase in Eudragit L100 particle mean size observed with the amount of PVA could be explained by the aggregation phenomenon induced by depletion during the nucleation step. Particles aggregation was confirmed by observations realized on resulting samples using optical microscope. The colloidal stability of the dispersions is thus determined by a balance between repulsive electrostatic forces and the particles aggregation induced by depletion.

However, for Eudragit E100, no significant change in particle size was observed as the mean size of the formed particles remains around 40-50 μm and the zeta potential was not affected (around 20 mV). This can be explained by the dominance of repulsive electrostatic forces between particles induced by the high cationic character of Eudragit E100.

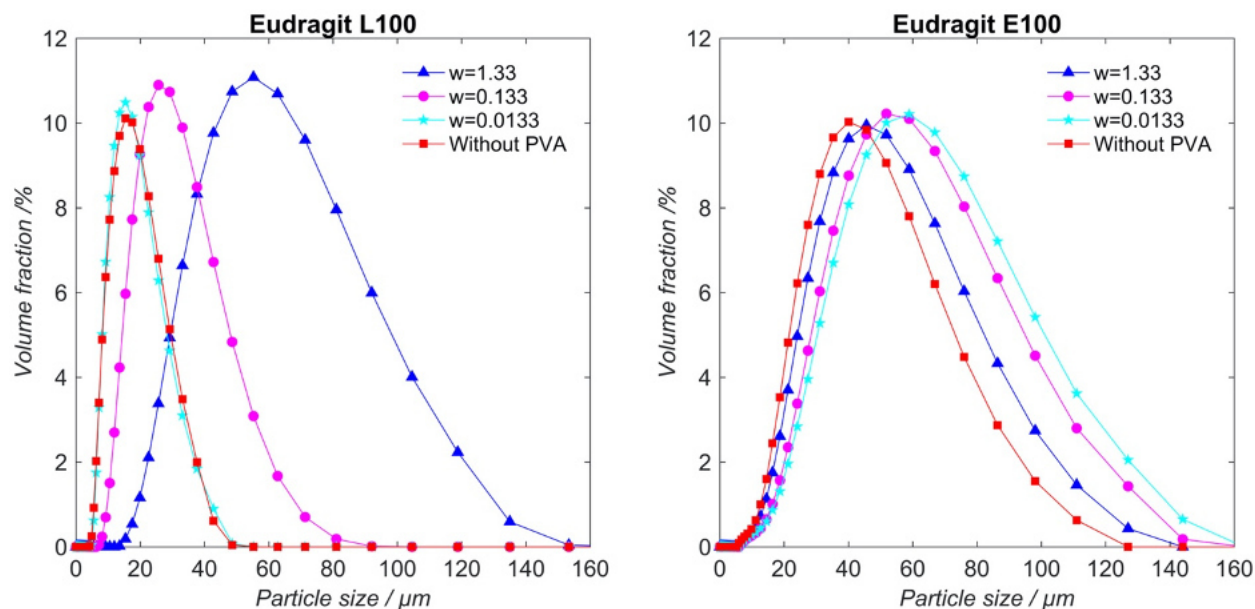


FIGURE 4.1 – Volume-based hydrodynamic particle size distribution of particles formed in presence of PVA as a function of w ratio.

4.3.5 Influence of Pluronic F68

The effect of the non-charged surfactant polyoxyethylene-polyoxypropylene block copolymer (Pluronic PF68) on Eudragit L100 and Eudragit E100 precipitation was investigated. As shown in Figure 4.2, similar tendency as for PVA was observed in the presence of Pluronic PF68. Basically, the increase in PF68 amount leads to an increase in the mean hydrodynamic size of precipitated Eudragit L100 particles. In fact, the mean size increases from around 15 μm to 60 μm when the ratio w increases from 0 to 1.33 (%wt.). Moreover, the zeta potential tends to zero with the increasing amount of PF68.

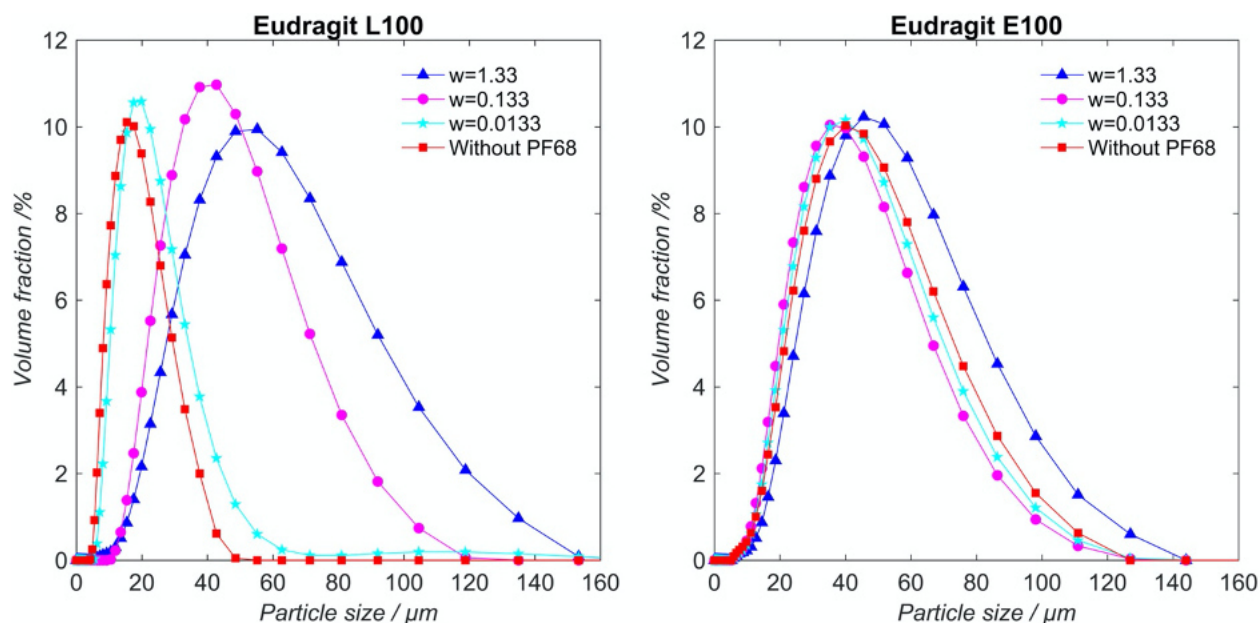


FIGURE 4.2 – Volume-based hydrodynamic particle size distribution of particle formed in presence of Pluronic PF68 as a function of w ratio.

As for PVA, these values are related to the reduction of surface charges by the presence of the non-charged polymer which induces screening effect of surface charges or the adsorbed PF68 amount leads to shift in the shear plan position far from the surface leading to low zeta potential in absolute value. As described for PVA before, aggregation phenomenon can explain this increase in mean particle size.

However, for Eudragit E100, no significant change in the particle mean hydrodynamic size was noticed with unvaried value of the zeta potential (around 25 mV). This can be attributed to the high polyelectrolyte character of E100 compared to L100. In fact, E100 is more charged and leads to low particle size compared to L100. The observed negative zeta potential can be attributed to hydroxyl groups condensation surrounding the particles. Similar negative zeta potential has been observed in the case of both amine and amidine containing polystyrene particles as reported by Ganachaud et al. [36].

4.3.6 Influence of Polyethylenimine (PEI)

The effect of the positively charged polyethylenimine (PEI) on precipitation of both Eudragit L100 and E100 was investigated according to the experimental conditions reported in Table 4.2. As it can be noticed from Figure 4.3, PEI strongly impacts the size distribution of the precipitated Eudragit L100 particles for $w=1.33$ (%wt.). For this value of w , a stable suspension was obtained since the precipitated particles do not aggregate and consequently do not sediment. The resulting suspension showed a narrow size distribution around 200 nm and SEM images (Figure 4.4) showed a perfect spherical morphology and individual particles. The zeta potential of the particles measured at pH=7 was found to be highly positive (+45 mV) which ensures the good colloidal stability of the elaborated particles and reflects also the presence of PEI on the particles surface. The obtained particles are comparable in size with PMMA-PEI core-shell particles prepared by Pei Li's team [17, 18, 37] using graft copolymerization process for gene delivery. In fact, they obtained PMMA-PEI core-shell monodispersed particles (172 ± 7 nm), spherically shaped with a highly positive zeta potential (50.3 ± 2.6 mV).

More generally for Eudragit L100 dispersions, an increase of the zeta potential can be noticed with the increase of the amount of PEI. It can be suggested that PEI which is a positively charged polyelectrolyte may coprecipitate with Eudragit L100 and may also recover the Eudragit particles conferring them enough surface charges to avoid their aggregation.

Runs	[PEI] (g/l)	w %wt.	Final pH	Zeta potential (mV)
L100				
	1.25	1.33	8.16	+45.3
	0.125	0.133	2.97	+30.9
	0.0125	0.0133	2.78	-2.81
	0	0	2.84	-6.03
E100				
	* 1.25	1.33	8.29	4.18
	0.125	0.133	10.36	1.69
	0.0125	0.0133	10.55	-17.4
	0	0	10.36	-24

TABLE 4.2 – Precipitation of Eudragit L100 and E100 in presence of Polyethylenimine (PEI).
*Precipitation occurs directly with PEI solution without NaOH 10^{-2} M solution

Thus, PEI seems to be part of the resulting particles under the investigated conditions. This hypothesis is confirmed by the final pH of the suspension. Indeed, the resulting suspension for $w=1.33$ (%wt.) exhibits a pH value of 8.16, corresponding to the solubility domain of Eudragit L100. A previous experiment has shown that the PEI alone did not precipitate under the investigated experimental conditions.

Thus, the presence of PEI could modify the precipitation domain of Eudragit L100 leading to the preparation of particles involving Eudragit L100 and PEI. It can be suggested that an interpolyelectrolyte complex (IPEC) based on Eudragit L100 and PEI have then been prepared under a dispersed form.

When reducing the w value from 1.33 to 0.133 (%wt.), a highly polydisperse dispersion was obtained and for w value higher than 1.33 (%wt.) (data not shown here), a gel-like deposit was obtained in the precipitation medium. The minimal w value needed to ensure the preparation of stable dispersions with Eudragit L100 and PEI interpolyelectrolyte polyplex was then identified between 0.33 and 0.67 (%wt.) as it is shown by Dynamic Light Scattering measurements presented on Figure 4.5.

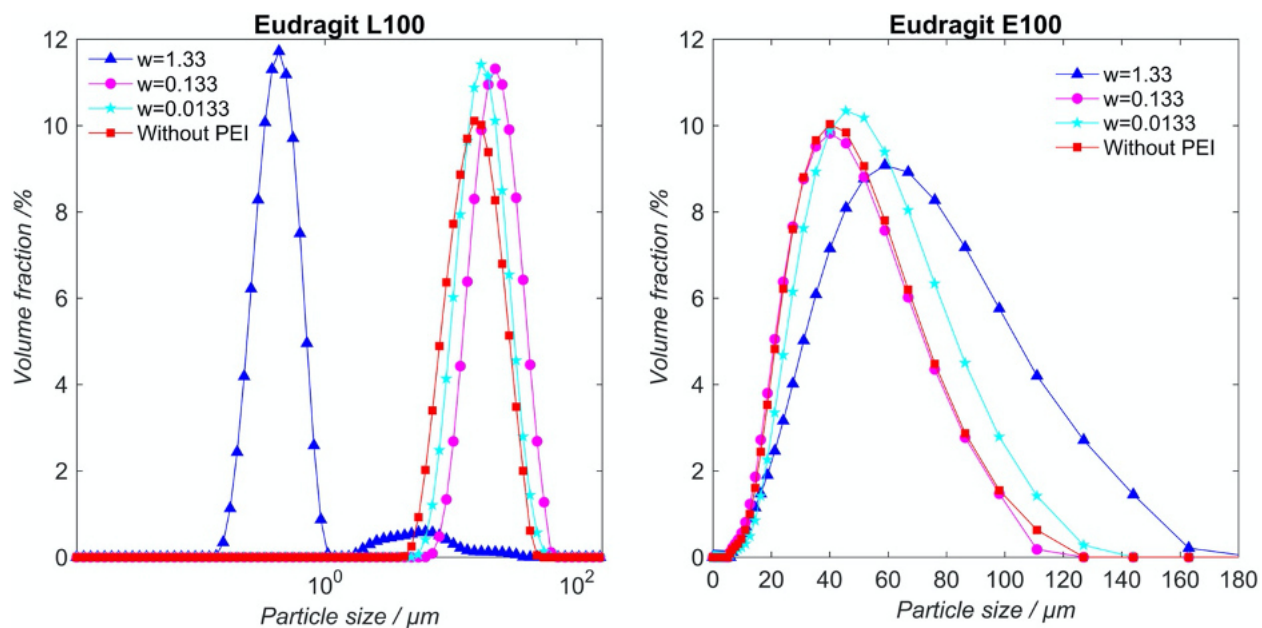


FIGURE 4.3 – Volume-based hydrodynamic particle size distribution of particle formed in presence of polyethylenimine (PEI) as a function of w ratio.

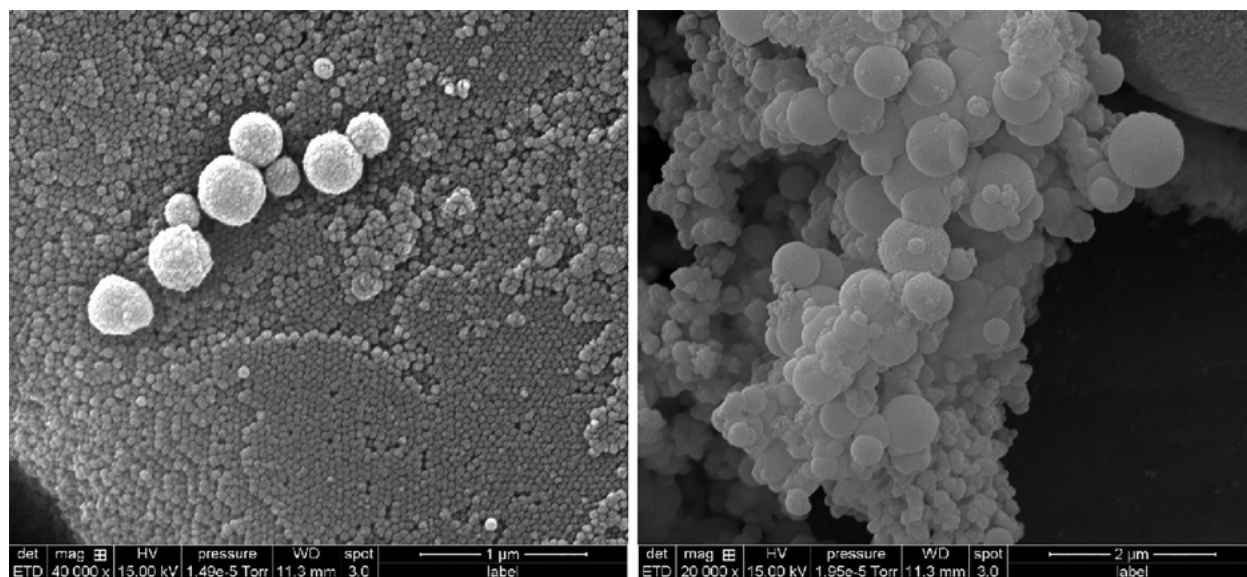


FIGURE 4.4 – SEM images of precipitated Eudragit particles in presence of polyethylenimine for $w=1.33$

For the experiment performed at $w=1.33$ (%wt.), polyethylenimine induces Eudragit E100 precipitation without adding a sodium hydroxide solution to the formulation, as above described for polyacrylic acid. The final pH of the suspension was 8.29, which corresponds to

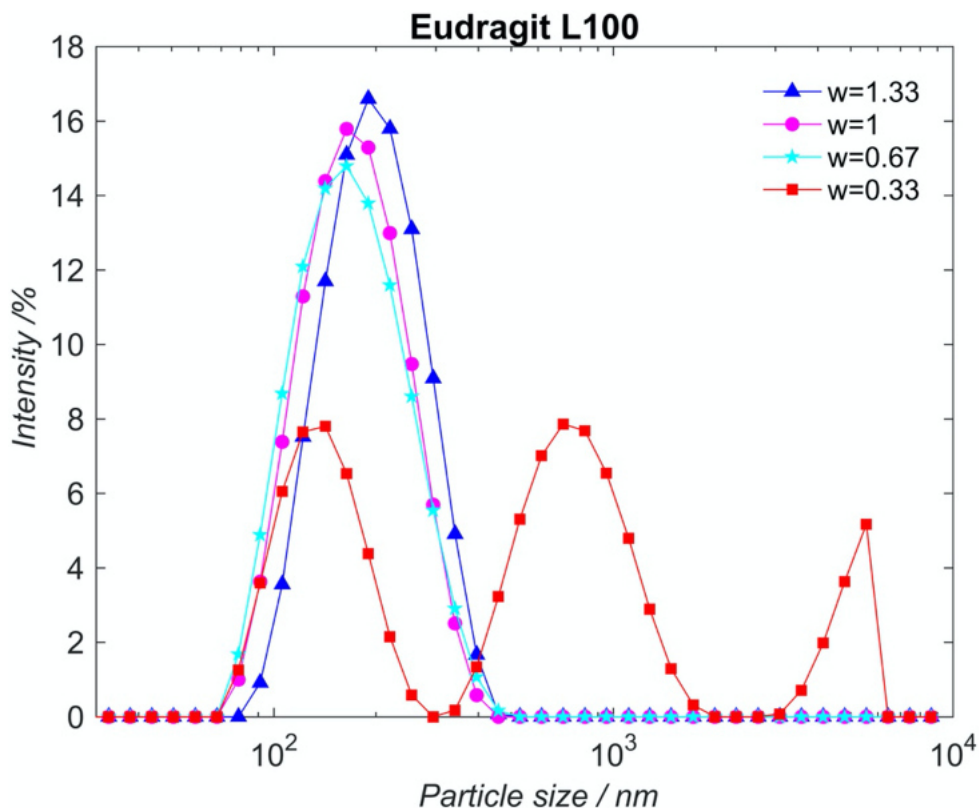


FIGURE 4.5 – Hydrodynamic particle size distribution of IPEC involving Eudragit L100 and polyethylenimine (PEI) measured by DLS as a function of w ratio

the normal precipitation domain of Eudragit E100 [34]. The most likely hypothesis is that, as for polyacrylic acid, polyethylenimine solution (1%) led to basification of the medium and precipitation of Eudragit E100 according to its precipitation domain regardless to pH. In addition, since Eudragit E100 and PEI are both positively charged polyelectrolytes, IPEC formation could not occur in such conditions. Resulting particles present a zeta potential close to zero (+4.18 mV) measured at pH=8. This zeta potential value is probably due to the presence of PEI at the particles surface.

Regarding the effect of PEI on Eudragit E100 precipitation, it was found to be negligible as expected. This can be attributed to the repulsive electrostatic interactions between both polymers and consequently no direct effect on Eudragit E100 precipitation. The presence of PEI in the precipitation medium does not seem to induce any depletion phenomenon since

no effect on particles size, size distribution and colloidal stability has been revealed.

Regarding the measured zeta potential, it is worth mentioning that, the reported zeta potential values are not measured in the same conditions in terms of pH. The presence of free PEI in the medium affects the salinity by increasing its value and consequently, the zeta potential decreases in absolute value as expected theoretically.

4.3.7 Influence of amino-dextran (AMD)

As well known, polysaccharides may be involved in hydrogen binding when mixed with charged or potentially ionizable water soluble polymers. Then, the effect of amino dextran, which is a cationic polyelectrolyte on the precipitation of Eudragit L100 and Eudragit E100 was separately investigated. Surprisingly, amino-dextran seems to have no influence on the precipitated Eudragit L100 for w values of 0.133 and 0.0133 (%wt.). However, for a value of 1.33 (%wt.), large particles (around 375 μm) and large polydispersity were pointed out by light diffraction measurements (data not shown). The observed positive zeta potential can be attributed to the cationic character of the formed objects. This can be attributed to a slight incorporation of amino dextran on the particles surface. Indeed, an increase of the zeta potential value was observed (from -6 mV to +14 mV when increasing the AMD amount (from w values of 0 to 1.33 %wt.)). Regarding the effect of amino dextran on the precipitation of Eudragit E100, it was found to be totally marginal even though an increase of the zeta potential values was observed (from -24 mV at $w=0$ to +14 mV at $w=1.33$ %wt.). As for Eudragit E100/PEI, similar observations and interpretations are valid here for Eudragit E100/amino-dextran system.

4.4 Conclusion

In this work, the influence of various secondary polymers on the precipitation of Eudragit L100 and E100 was investigated. The effect of six selected non-charged (polyvinyl alcohol, dextran 40, Pluronic F68) and charged (negatively charged polyacrylic acid and positively charged polyethylenimine, amino-dextran) polymers is reported. Various trends can be deduced from the obtained results : almost no effect of non-charged polymers has been noticed which explains that these polymers do not act as stabilizing agent during the particles nucleation step and do not induce any depletion phenomenon which may affect the colloidal stability of the formed dispersions from Eudragit E100. Regarding the Eudragit L100, whatever the secondary polymer amount, dextran T-40 and polyacrylic acid have no influence on the size distribution of the precipitated particles. Whereas, in presence of PVA and Pluronic F68, an increase in the particle mean size was observed due to aggregation phenomenon. Concerning the use of a secondary polymer of the same charge as the main polymer, no effect has been observed and even no depletion phenomenon has been revealed. Regarding the oppositely charged polymers, the size, size distribution and zeta potential have been affected which explains the attractive electrostatic interactions involved in the nucleation process or even after particles formation.

Interestingly, the addition of highly positively charged electrolytes showed interesting results. In fact, polyethylenimine (PEI) was found to allow the preparation of Eudragit L100 dispersion of 200 nm hydrodynamic mean size, spherically shaped with a narrow size distribution as pointed out by SEM images. Surprisingly, opposite systems such as polyacrylic acid with Eudragit E100 do not lead to expected stable dispersions.

Conflict of interest

The authors declare no conflict of interest.

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Chapitre 5

INTERACTIONS ET COMPLEXATION DES DERIVES DE POLYMETHACRYLATES EUDRAGIT E100 ET L100 AVEC DES TENSIOACTIFS EN SOLUTION AQUEUSE

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En solution aqueuse, les polyélectrolytes peuvent présenter des interactions avec les tensioactifs et peuvent conduire à la formation de complexes polymères-tensioactifs [1, 2, 3] présentant un certain nombre d'applications dans des domaines tels que la fabrication des détergents [4, 5], l'industrie cosmétique [6], l'industrie pharmaceutique [7], l'industrie pétrolière [8] etc. C'est dans ce sens que s'inscrit la troisième partie de notre travail expérimental. Elle traite en effet des interactions Eudragit-tensioactifs et il est question d'étudier la possibilité de développer un nouveau procédé et produire ainsi une nouvelle génération de particules [9]. Nous avons à cet effet procédé à l'étude des interactions pouvant avoir lieu entre les Eudragit E100 et L100 d'une part et différents tensioactifs d'autres parts. Les différentes catégories de tensioactifs ont été explorées. Nous avons donc procédé à cette étude avec un tensioactif non-ionique (le polyéthylène glycol tert-octyl phenyl ether ou Triton X-100), un tensioactif zwitterionique (le 3-(*N*, *N*-Diméthyl myristyl ammonio) propane sulfonate ou SB3-14), un tensioactif anionique (Dodécyl Sulfate de Sodium ou SDS) et un tensioactif cationique (le Bromure de Cetyl Triméthyl Ammonium ou CTAB). L'influence de la concentration en tensioactif, du pH et de la salinité sur la solubilisation et la précipitation des complexes Eudragit-tensioactif est étudiée. Les dispersions obtenues suite à des séparations de phases ont été caractérisées en termes de distribution de taille de particules et de potentiel zêta.

Les Eudragit E100 et L100 sont d'abord solubilisés respectivement dans de l'acide chlorhydrique et dans la soude pour des pH de solubilisation respectifs de 2,5 et 7 sur la base des résultats de notre première étude. Les solutions de tensioactifs sont préparées à ces deux valeurs de pH et à différentes concentrations et mélangées ensuite aux solutions d'Eudragit de sorte que toute séparation de phase ne soit pas imputable à une modification du pH du milieu. Des concentrations autour de la concentration micellaire critique (CMC) des tensioactifs sont étudiées. Dans un second temps, différents pH (gamme de pH allant de 0 à 2,5 pour l'Eudragit E100 et de 7 à 14 pour l'Eudragit L100) et différentes concentrations en sel ont été explorés (0 à 1000 mM). Comme pour les études précédentes, la distribution de taille des

particules a été obtenue par diffusion dynamique de la lumière pour les dispersions submicro-
niques et par diffraction de la lumière pour les dispersions micrométriques. Le potentiel zêta
des particules préparées pour les différentes dispersions obtenues a été mesuré pour une va-
leur de salinité et de pH donnée, les deux copolymères étudiés étant sensibles au pH du milieu.

Le tensioactif non ionique Triton X-100 n'a montré aucun effet sur les Eudragit E100 et
L100 en solution pour des concentrations allant de 0,1 à 5 mM (17-30 fois la valeur de la CMC)
et pour les pH étudiés (pH= 0 à 2,5 pour E100 et pH =7 à 14 pour L100). Ceci s'explique
par l'absence totale d'interactions entre les deux copolymères solubilisés et le Triton X-100
non ionique et non chargé en solution. Un peu plus surprenant, cette absence d'interaction
a également été observée avec le SB3-14, tensioactif zwitterionique pour des concentrations
allant de 0,1 à 50 mM (125 à 500 fois la valeur de la CMC). Les tensioactifs zwitterioniques
ou amphotères étant chargés à la fois positivement et négativement, on aurait pu s'attendre
à la formation de complexes menant à une séparation de phase avec les deux copolymères.
L'absence d'interaction entre 0,1 et 50 mM s'explique par le fait que les charges opposées de
ces molécules de tensioactifs se neutralisent permettant ainsi de garder les deux copolymères
à l'état soluble. Toutefois en augmentant considérablement la concentration en SB3-14 (100
mM soit 250 à 1000 fois la CMC), on a pu constater comme décrit dans la littérature pour
les systèmes polycation-tensioactif qu'une progressive séparation de phase se produisait pour
le système Eudragit E100/SB3-14.

S'agissant des tensioactifs ioniques, ceux présentant des charges contraires aux polyélectro-
lytes sont les plus à même de conduire à la formation de complexes polyélectrolyte-tensioactif
et à une séparation de phase. Ceci est lié à l'attraction électrostatique entre charges opposées
et à l'effet d'écrantage de charges qui réduisent la solubilité du polyélectrolyte. Ainsi des dis-
persions résultant de la précipitation ont été obtenues pour les systèmes Eudragit E100/SDS
et Eudragit L100/CTAB.

Pour le premier système Eudragit E100/SDS à pH=2,5 ; une séparation de phase s'opère pour un rapport de charges polymère/tensioactif compris entre 1,25 (4 mM SDS) et 2,5 (8 mM SDS) et les particules préparées sont submicroniques. Nous avons pu constater qu'à l'intérieur du domaine de précipitation, la taille moyenne des particules augmente pour atteindre une valeur maximale et ensuite diminue ($\simeq 40$ nm à 4 mM pour atteindre 600 nm vers 6 mM et redescendre à $\simeq 10$ nm à 8 mM). Le potentiel zêta des particules évolue de -26 à -40 mV (mesuré à pH=3) pour une concentration en SDS allant de 5 à 7 mM suffisant pour assurer une stabilité colloïdale aux dispersions. Au-delà de 8 mM (valeur moyenne de la CMC), nous avons observé une re-solubilisation des complexes due aux interactions avec les micelles qui la favorisent. L'effet de la salinité a été étudié pour des concentrations en NaCl allant de 0 à 1000 mM. Si en dessous de 50 mM, aucune influence significative de la concentration en NaCl n'a été notée, des particules de grande taille (voire des agrégats) ont été obtenues pour des concentrations allant de 100 à 1000 mM. Nous avons également pu voir qu'en travaillant dans des conditions plus acides (pH de 0 à 2,5) ; cela avait le même effet que l'augmentation de la salinité. En effet, nous avons noté une augmentation de la taille des particules avec un domaine de précipitation élargi (3 à 15 mM et 3 à 25 mM respectivement à pH=1 et 0).

Pour le second système Eudragit L100/CTAB et à pH=7, la séparation de phase a lieu à partir d'une concentration en CTAB de 4,5 mM (5 fois la CMC) et un rapport de charges polyélectrolyte/tensioactif de 3,5 environ. Le domaine de précipitation s'étend de 4,5 à 8 mM (rapport de charges polymère/tensioactif allant de 2,5 à 3,5). Il est important de faire ressortir ici que la séparation de phase est contrôlée par le régime micellaire contrairement à ce qui a été observé dans le cas du système Eudragit E100/SDS. Aussi à l'intérieur du domaine de précipitation, la concentration en CTAB n'impacte pas la taille des particules qui sont dans l'ensemble submicroniques (taille moyenne en nombre autour de 500 nm). Nous avons noté une évolution du potentiel zêta de -26 à +20 mV (mesuré à pH=7) pour une

concentration en CTAB allant de 4,5 à 6 mM, ce qui montre que le tensioactif participe bien à la structure des particules obtenues. Au-delà de 8 mM, la concentration en CTAB devient suffisante pour favoriser la re-solubilisation des complexes plutôt que la séparation de phase. L'effet de la salinité a été étudié pour des concentrations en NaCl allant de 0 à 1000 mM. A de faibles concentrations en NaCl (0 à 10 mM), aucun effet significatif n'a été observé sur les particules d'Eudragit L100/CTAB. Autour de 50 mM, nous avons observé un phénomène d'agrégation des particules. De plus, pour des concentrations en NaCl supérieures à 50 mM, aucune séparation de phase ne s'est opérée. Ceci peut être lié à un écrantage des interactions électrostatiques attractives et à une possible réduction de la CMC du CTAB conduisant à une possible modification de l'intervalle de précipitation en raison de la présence d'une très grande quantité de sel. En opérant à des pH plus basiques pour l'Eudragit L100, des agrégats de particules sont obtenus. L'effet observé est le même que ce que nous avons obtenu pour une concentration en sel de 50 mM. Cette observation serait donc due à l'augmentation de la force ionique. Par ailleurs, un léger élargissement du domaine de précipitation a été observé (4 à 10 mM aux pH 13 et 14).

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POLYMETHACRYLATE DERIVATIVES EUDRAGIT E100 AND L100 : INTERACTIONS AND COMPLEXATION WITH SURFACTANT

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Abstract :

Precipitation or coprecipitation of polyelectrolytes has been largely investigated. However, the precipitation of polyelectrolytes via addition of charged and non-charged surfactants has not been systematically studied and reported. Consequently, the aim of this work is to investigate the effect of different surfactants (anionic, cationic, non-charged and zwitterionic) on the precipitation of cationic and anionic polymethyl methacrylate polymers (Eudragit). The surfactants effect has been investigated as a function of their concentration. Special attention has been dedicated to the CMC range and to the colloidal characterization of the formed dispersions. Moreover, the effect of salt (NaCl) and pH was also addressed. It is pointed out that non-ionic and zwitterionic surfactants do not interact with charged Eudragit E100 and L100. For oppositely charged Eudragit E100/SDS and Eudragit L100/CTAB, precipitation occurs, and the obtained dispersions have been characterized in terms of particle size distribution and zeta potential. It was established that the binding of SDS molecules to Eudragit E100 polymer chains is made through the negative charges of the surfactant heads under the CMC value whereas binding of CTAB to Eudragit L100 chains is made at a CTAB concentration 5 times above its CMC. For Eudragit E100/SDS system, a more acidic medium induces aggregation. A same result was observed for the Eudragit L100/CTAB at a more basic pH. Moreover, it was observed that increasing salt concentration (higher than 100 mM) led to aggregation as generally observed for polycations/anionic surfactant systems.

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Keywords : Polyelectrolyte, polyelectrolyte-surfactant complexes, precipitation, pH-sensitive polymers, Eudragit.

5.1 Introduction

Polymers are nowadays used in various fields and are formulated in different ways according to the intended application. In fact, polymers find application in automotive and transport [1], electricity and electronics [2], building and civil engineering [3], cosmetics and fashion industry [4, 5], packaging and food engineering [6, 7, 8], medicine and health [9, 10] etc. For the latter application domain, the preparation of polymeric matrices as therapeutic vectors in the pharmaceutical industry is mostly based on precipitation methods using organic solvents [11]. Polymers can also be precipitated from aqueous medium in uncharged state with the risk of collapse associated to the structure of the polymer chains [12, 13].

Precipitation or coprecipitation of polyelectrolytes has been largely investigated. This is the case for a well-known class of polymers referred to as smart polymers which are sensitive to external stimuli such as pH, ionic strength, temperature, light, mechanical stress, electric and magnetic fields and ultrasounds [14]. These polymers react to surrounding environmental conditions and can be soluble/insoluble depending on the abovementioned stimuli and their intensity [15]. Precipitation/solubilization property of pH-sensitive polymers for instance finds application in drug delivery [16]. Another way of using polymers in drug delivery is through polyelectrolytes complexes (PECs). PECs are prepared by mixing cationic and anionic polymers in aqueous solutions with strong and reversible electrostatic interactions, conferring to the new elaborated coating material some specific properties [17]. Moreover, advances in drug delivery systems and polymer science have led to the development of another type of complexes known as polymer-surfactant complexes. In fact, polyelectrolyte-surfactant

complexes (PESCs) find application not only in pharmaceutical formulations [18] but also in detergency [19], cosmetics [20], wastewater purification [21, 22, 23], rheological control [24, 25] and in surface adsorption, biofuel extraction and oil recovery [26] and surface adsorption [27]. It was evidenced that surfactants performance could be bolstered with polymers addition. PESCs formation is known to be driven by electrostatic interactions between polymer chains and surfactant head groups that result in hydrophobic complexes [28, 29]. Mixtures of oppositely charged polymers and surfactants are prone to induce this kind of complexes. The process usually occurs at a surfactant concentration called the critical aggregation concentration (CAC), which is several orders of magnitude below the critical micelle concentration (CMC). Electrostatic interactions are influenced by the pH, the surface charge density, and the salt concentration whereas hydrophobic interactions are sensitive to chain length, molecular weight or structure of the polyelectrolyte chains or surfactants tail. PESCs properties depend on surfactant concentration and mixing conditions as well. Altering these parameters induces macroscopic changes in the resulting nanosystems [30].

Poly (diallylammonium chloride) (PDADMAC) mixtures with different surfactants have been largely studied. This is due to the use of these mixtures in shampoo and hair conditioner formulations [31, 32]. Studies on polyacrylic acid (PAA) and poly methacrylic acid (PMA) interactions with surfactants have also been reported in literature [12, 13, 28, 33, 34, 35, 36]. PESCs involving oppositely charged PAA and DoTab [37] or C_{14} TAB [28] studies showed that their formation is related to the enhancement of hydrophobicity upon surfactant binding onto polymer chains. Furthermore, these studies reported the tendency of complex-complex interaction enhancement leading to the formation of aggregates and their gradual dissolution by increasing PAA molecular weight (MW) or in presence of surfactant excess. Deh-Ying Chu and J. K. Thomas established that there is a significant effect of the surfactant chain length and polyelectrolyte concentration on the CAC based on interactions between PMA and alkyl trimethylammonium bromide C_n TAB cationic surfactants [33]. Moreover, Y. Li et al. inves-

tigated the interactions between Sodium Dodecyl Sulfate (SDS) and polyethylenimine (PEI) and some ethoxylated PEI [38]. They have firstly observed that for this system, the CAC of SDS decreases with decreasing pH. They have further seen that SDS concentration range over which phase separation occurs decreases as the size of the ethoxylated chains increases. For the polymer with the longest ethoxylated chain, no precipitation occurs, and the number of bound surfactant molecules per mole of polymer is independent of pH.

We previously investigated the effect of physico-chemical parameters such as pH, salinity, polymer concentration, and incubation time on the solubility and the precipitation of two oppositely charged polymethylmethacrylate derivatives namely Eudragit L100 and Eudragit E100 [15]. Moreover, we studied the influence of a secondary polymer on the direct precipitation of these two polymers [17]. Eudragit L100 chains when solubilized present a negative charge due to the dissociation of carboxylic groups into COO^- . Regarding Eudragit E100, its chains exhibit a positive charge due to the protonation of amine groups present in their structure (NH_4^+). Moreover, titration curves revealed two equivalences that helped estimating carboxylic content of Eudragit L100 (6 mmol/g) and ammonium content of Eudragit E100 (4 mmol/g). Starting from these preliminary results, the aim of the present work is to study charges screening effect of oppositely charged surfactants on the precipitation of the two Eudragit polymers. Formation and precipitation of PESCs, effect of pH and salt are studied and discussed throughout this work.

5.2 Materials and methods

5.2.1 Materials

Eudragit L100 (methacrylic acid - methyl methacrylate copolymer (1 :1)) powder ($M_w=125000$ g/mol) and Eudragit E100 (dimethyl aminoethyl methacrylate, butyl methacrylate, and methyl methacrylate tri-copolymer with a ratio of 2 :1 :1) pellets ($M_w=47000$ g/mol)

were obtained from Evonik Röhm GmbH (Darmstadt, Germany). Sodium hydroxide was a product from Sigma Aldrich (Sweden) and hydrochloric acid (35%) was purchased from VWR Chemicals (France). Sodium chloride was obtained from Laurylab (Brindas, France). Sodium dodecyl sulfate (SDS) purchased from Sigma Aldrich (USA), Hexadecyltrimethylammonium bromide (CTAB) from Alfa Aesar (Germany), polyethylene glycol tert-octyl phenyl ether (Triton X-100) from Fisher bioreagents (USA) and 3-(*N,N*-Dimethyl myristyl ammonio) propane sulfonate (SB3-14) from Sigma Aldrich (China) were used as surfactants. Figure 5.1 presents the chemical structures of the studied polymers. Table 5.1 summarizes some characteristics of the studied surfactants and Figure 5.2 gives their chemical structure.

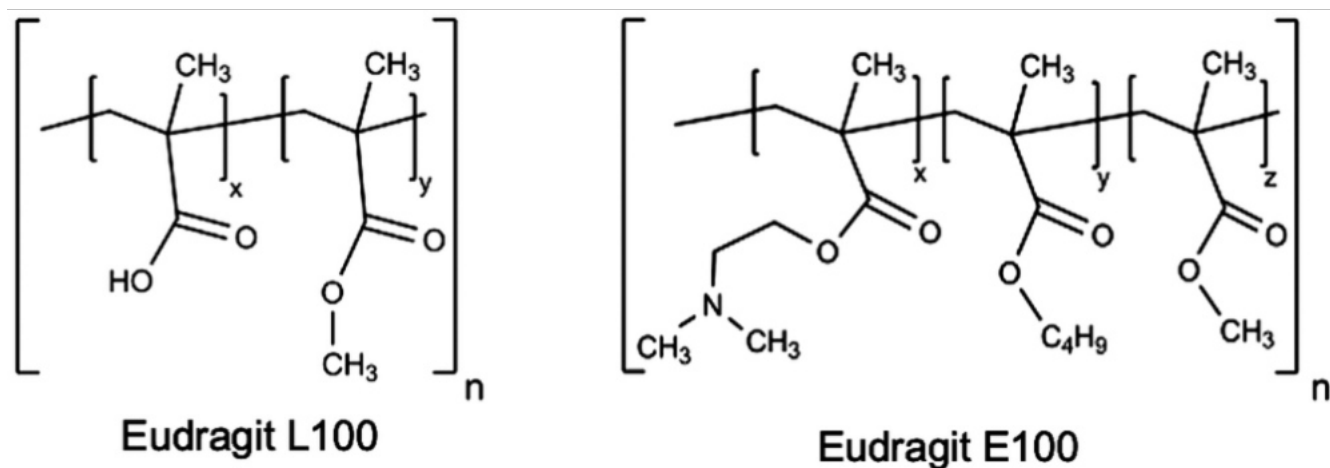


FIGURE 5.1 – Molecular structures of Eudragit L100 and Eudragit E100.

5.2.2 Methods

Samples preparation

All mixtures, solutions and samples were prepared and stored at room temperature. Eudragit L100 powder and Eudragit E100 pellets were firstly solubilized respectively in NaOH and HCl at a concentration of 2.5 g.L⁻¹. Three final solubilization pH values were achieved for each polyelectrolyte (7, 13 and 14 for L100 and 2.5, 1, and 0 for E100). Surfactant solutions were prepared by solubilization in a medium prepared at the solubilization pH of the

Surfactant	Type	CMC (mM)	MW (g.mol ⁻¹)
Sodium Dodecyl Sulfate (SDS)	Anionic	7-10	288.4
Hexadecyl trimethyl ammonium bromide (CTAB)	Cationic	0.9	364.5
4-(1,1,3,3-Tetramethylbutyl) phenyl-polyethylene glycol (Triton X-100)	Non-ionic	0.17-0.3	630
3-(N,N Dimethyl myristyl ammonio) propane sulfonate (SB3-14)	Zwitterionic	0.1-0.4	363.6

TABLE 5.1 – Some characteristics of the investigated surfactants [39].

corresponding Eudragit polymer. Dilutions are then prepared to obtain the desired surfactant concentrations without pH variation. For low solubility surfactants such as CTAB, a slight heating was needed, and the experiments were realized quickly before any crystallization. If needed, a further slight heating was achieved before solution mixing.

Surfactant solutions were then mixed with polymer solutions in equivalent volumes in a one-shot procedure under continuous stirring at a rate of 500 rpm. It was shown that “one shot” or “stop-flow” mixing procedure resulted in PESC’s particles that were much smaller in size and stable enough to be measured contrary to the dropwise or “slowly added” mixing method [40]. Moreover, it was shown that the smaller particles formed by the “surfactant to polymer” mixing method were more resistant to electrolytes induced colloidal instability than the larger ones formed by “polymer to surfactant” addition [41]. Different concentrations were tested for each surfactant by screening around its CMC whereas the polyelectrolyte concentration was kept constant at 0.125 wt.% in final samples. The pH of all surfactant solutions was adjusted to that of the corresponding polymer solution so that any further precipitation could not be linked to pH conditions. In a typical experiment, 40 mL of surfactant solution were added to 40 mL of polymer solution. Precipitation and polymer-surfactant

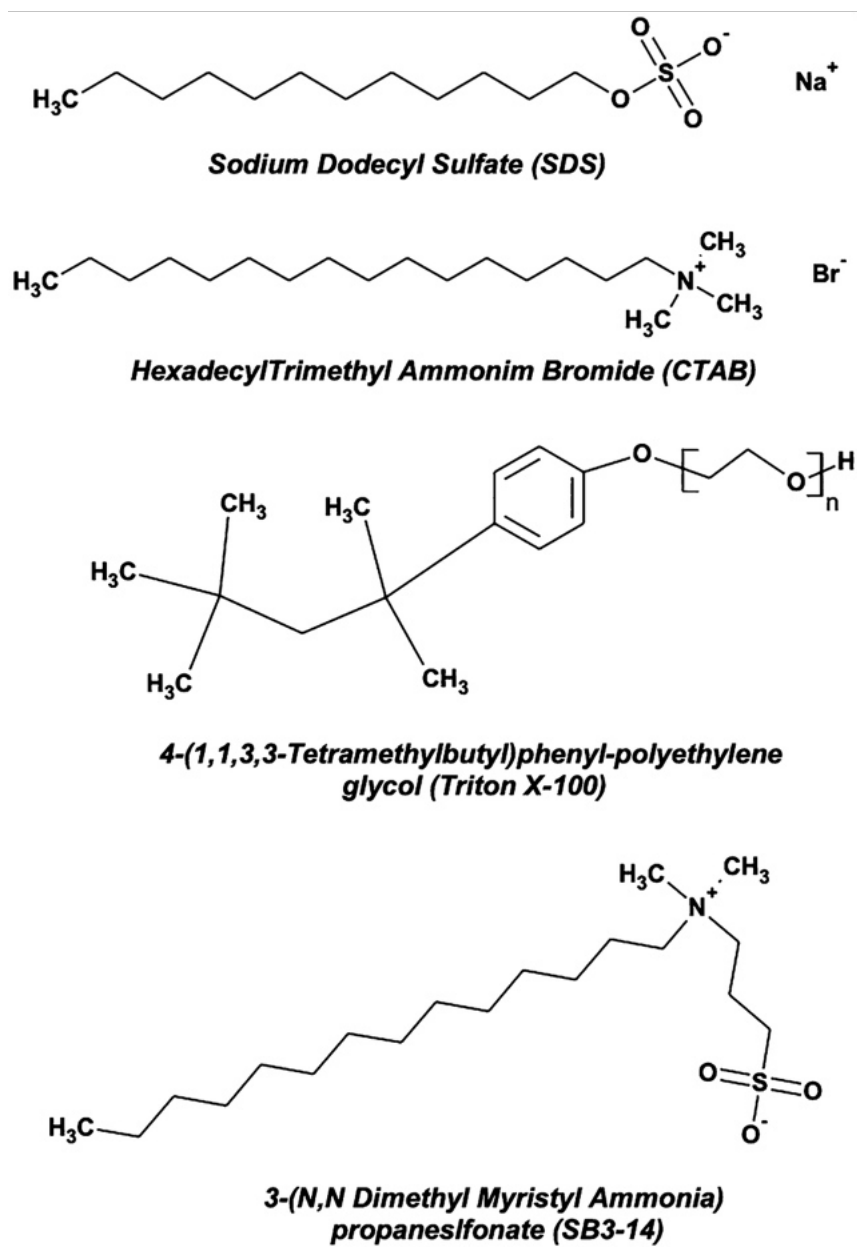


FIGURE 5.2 – Chemical structure of the investigated surfactants.

complex formation was evaluated by macroscopic observation through turbidity appearance. The resulting suspensions were maintained under stirring for 30 minutes and were further characterized in terms of size distribution and zeta potential.

Samples characterization

Particle Size Distribution (PSD) Hydrodynamic mean particle size and size distribution of the precipitated polymers were determined by Dynamic Light Scattering (DLS) using a Zetasizer Nano ZS (Malvern Instruments) in the case of submicron particles and by light diffraction using a Mastersizer 3000 (Malvern Instruments) in the case of micrometric sized particles. Measurements were performed in deionized water for light diffraction and in 10^{-3} M sodium chloride deionized water solution for DLS.

Zeta potential measurement Zeta potential (ZP) was deduced from electrophoretic mobility measurement of all obtained suspensions using a Zetasizer Nano ZS (Malvern Instruments, France). Measurements were performed at room temperature, pH of the prepared samples, in 10^{-3} M NaCl medium and under effective voltage of 149 V automatically set by the device. Each value is the average of more than 5 runs.

5.3 Results and discussion

5.3.1 Non-ionic surfactant : Triton X-100

The non-ionic surfactant effect on the cationic and anionic polyelectrolytes was investigated as a function of surfactant concentration. Surprisingly, no marked effect was observed irrespective of the polymer charge nature. For Eudragit E100 and L100, the investigated Triton X-100 concentration ranging from 0.1 mM to 5 mM (17-30 times the CMC value) revealed no precipitation of both polymers for the considered pH range (pH=7 to 14 for L100 and pH=0 to 2.5 for E100). This can be attributed to a total lack of interaction between the polyelectrolytes and Triton X-100. In fact, Triton is a non-charged surfactant and both polyelectrolytes are soluble in the investigated pH ranges. This can also be attributed to static microstructure of the used polymers (E100 & L100). The same results were obtained by E. Fegyver and R. Mészáros [42] regarding the interactions taking place between

PDADMAC and nonionic surfactants *n*-dodecyl- β -D-maltoside ($C_{12}G_2$) and *n*-dodecyl-hexaethylene-glycol ($C_{12}E_6$). Moreover, Nagarajan analyzed the binding of poly (ethylene oxide) (PEO) to Triton X which presents a bulky neutral head [43]. He found that complexation was not favored due to free micelles formation instead of polymer-surfactant complexation. Based on this observation, the absence of interaction between Eudragit E100/L100 polyelectrolytes and Triton X-100 could be attributed to the high water molecules-polymer interactions in the investigated pH domain irrespective of Triton X-100 concentration.

5.3.2 Zwitterionic surfactant : SB3-14

Phase behavior of polymers and zwitterionic surfactant mixtures has gained interest during the last decade. This is due to recent international regulation for a safe and healthy use of chemical compounds in consumer products. They recommended indeed a progressive replacement of charged molecules, either polymers or surfactants, by neutral or zwitterionic ones [44]. In the present study, various SB3-14 zwitterionic surfactant (containing anionic carboxylate and cationic ammonium) concentrations were mixed with Eudragit E100 and L100 solutions. As for the non-ionic surfactant reported earlier, no effect has been observed irrespective of polymer nature, surfactant concentration ranging from 0.1 to 50 mM (corresponding to 125-500 times the CMC value) and investigated pH domain (pH=7 to 14 for L100 and pH=0 to 2.5 for E100). This result is quite surprising since this kind of surfactant exhibits both positive and negative charges making it suitable to interact basically with both polymers. The charge of the used polyelectrolyte is screened by the opposite charge of the zwitterionic surfactant. Instead of the polymer precipitation, the second residual charge of the surfactant promotes its solubilization. Consequently, as a result, the mixture solutions remain clear irrespective of surfactant concentration.

This observation is similar to the result obtained by E. Guzmán et al. [45] who noticed that there was no phase separation in mixtures of PDADMAC with sulfate-free zwitterio-

nic surfactant coco betaine (CB) (i.e. no any observed opalescence). Their results confirmed by DLS and electrophoretic mobility measurements were explained by taking into account the zwitterionic aspect of the hydrophilic surfactant head. Indeed, the headgroup of this surfactant exhibits at the same time anionic carboxylate and cationic ammonium. Our observations are also in agreement with the results reported by O.Pyshkina et al. [46]. By mixing poly(*N*-ethyl-4-vinylpyridinium bromide) and a zwitterionic surfactant (*n*-Dodecyl-(3-sulfopropyl)ammonium), the resulting solutions remain transparent in a wide range of surfactant/polymer molar ratios (from 0.1 to 200). Further addition of sodium bromide produces charges screening leading to complexation and phase separation. They suggest the formation of a coacervate complex between the polycation and the zwitterionic surfactant at concentrations above its CMC.

Akanno et al. [47] suggested the presence of two different regimes for PDADMAC - zwitterionic surfactant binding. The first one concerns low surfactant concentrations where zwitterionic surfactant molecules bind to the polymer chains. At this stage, there is no significant charge neutralization (each neutralized charge is counteracted by the positive charge present in the surfactant molecule). The second regime is at high concentrations (molar ratio polymer/surfactant equal to 1) where surfactant binding occurs through micelles which enables a real neutralization of PDADMAC charges. Thus, they showed the existence of polyelectrolyte-zwitterionic surfactant complexation for a very high surfactant concentration. They observed a significant micelle induced complexation for a mixture of PDADMAC and coco-amidopropyl-betaine only for a surfactant concentration 333 times (100 mM) the CMC value. Evidence of polymer-surfactant complex formation was only found when the number of surfactant molecules was close to the number of charged monomers in solution. Surfactant micelle negative charges interact with polymer monomers. The same result tendency was observed in micelle formation regimen for a mixture of SB3-14 with polycationic Eudragit E100 for a surfactant concentration of 100 mM (250-1000 times the CMC value). At the same

SB3-14 concentration, no precipitation occurred while working with polyanionic Eudragit L100.

5.3.3 Anionic surfactant : SDS

The effect of SDS on precipitation of both Eudragit E100 and L100 was investigated in the range of 1 mM to 20 mM (2-3 times its CMC value). All mixtures performed using Eudragit L100 exhibit a clear aspect which is explained by a total absence of interactions between both negatively charged SDS and Eudragit L100. This can be attributed to non-attractive interaction. As expected, due to negative charge of both Eudragit L100 and SDS, attractive electrostatic interactions are excluded. This also shows absence of hydrophobic interactions.

However, the effect of SDS on Eudragit E100 was found to be more relevant. From experiments performed at pH=2.5, three SDS concentration domains are pointed out. For low concentrations (< 4 mM), the amount of SDS is not sufficient to induce any screening effect. When the SDS concentration reaches 4 mM, milky like dispersions were obtained revealing the precipitation of Eudragit E100 (Figure 5.3). This is due to the sufficient SDS amount for the screening of Eudragit E100 charges and consequently reducing the solubility of the polyelectrolyte which induces polymer precipitation. Eudragit E100 positive charges are screened by SDS negative charges leading to precipitation following the scheme proposed in Figure 5.4.

Normally, for this surfactant/polymer charge ratio (0.4), the zeta potential should correspond to the isoelectric point. Above this SDS concentration, the formed SDS micelles interact with the positive charges of the polymer. Then, instead of charge screening, the immobilized micelles on the polymer via attractive electrostatic interactions enhance the solubilization of the SDS-polymer complexes.

The obtained dispersions (milky like dispersions) in the precipitation domain discussed

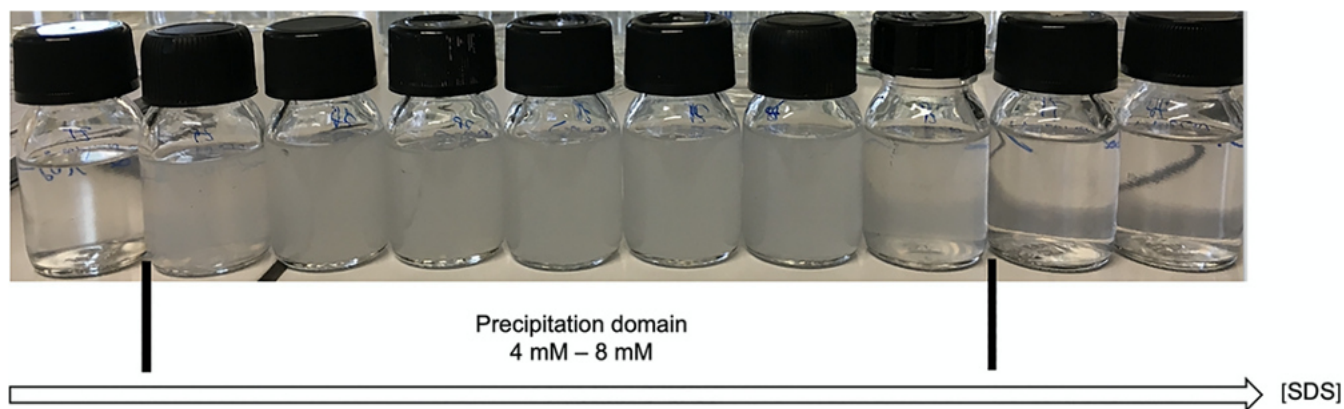


FIGURE 5.3 – Picture showing the three SDS interaction domains with Eudragit E100. Left : SDS concentration < 4 mM, no screening effect, no precipitation. Middle : complexation and Eudragit E100/SDS precipitation (4-8 mM). Right : Complexes solubilization upon micelles formation beyond 8 mM.

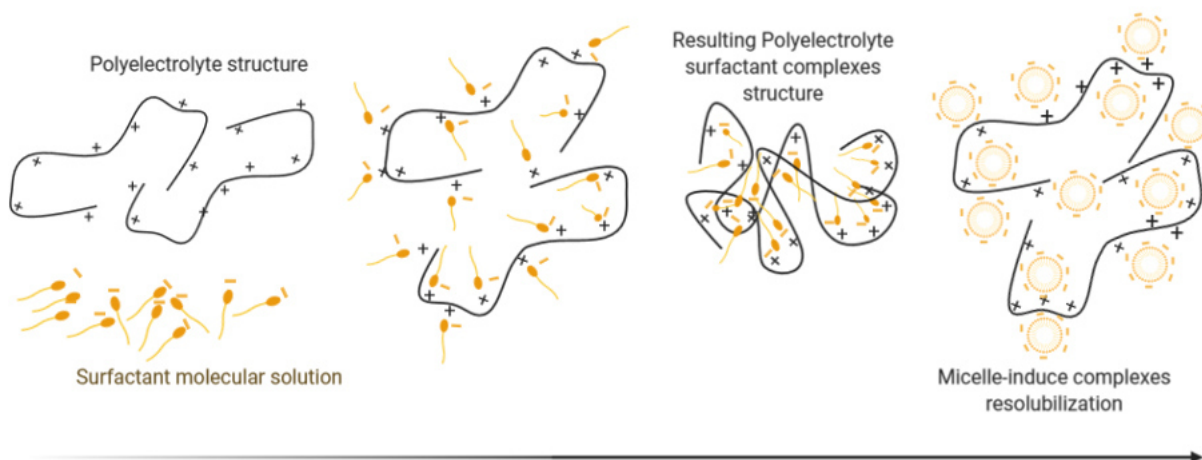


FIGURE 5.4 – A scheme illustrating interactions between positively charged Eudragit E100 chains and negatively charged SDS molecules headgroups as a function of SDS concentration. (a) SDS molecules binding to Eudragit E100 chains. (b) Polyelectrolyte chains collapse as Eudragit E100-SDS complex. (c) Complex resolubilization occurred in micellar regimen.

above are globally submicronic in size as illustrated in Figure 5.5 in which size distributions deduced from light scattering and diffraction are presented. Precipitation occurred for a polymer to surfactant charge ratio ranging from 1.25 to 2.5. The obtained hydrodynamic sizes from light scattering show both narrow size distribution and bimodal for 4 mM SDS concentration. But the average hydrodynamic size remains submicronic in nature. The optimum SDS concentration induces large particles size as determined via diffraction analysis, shows

narrow size distribution ranging from around 100 nm to 1000 nm, but remains submicronic too (Figure 5.5).

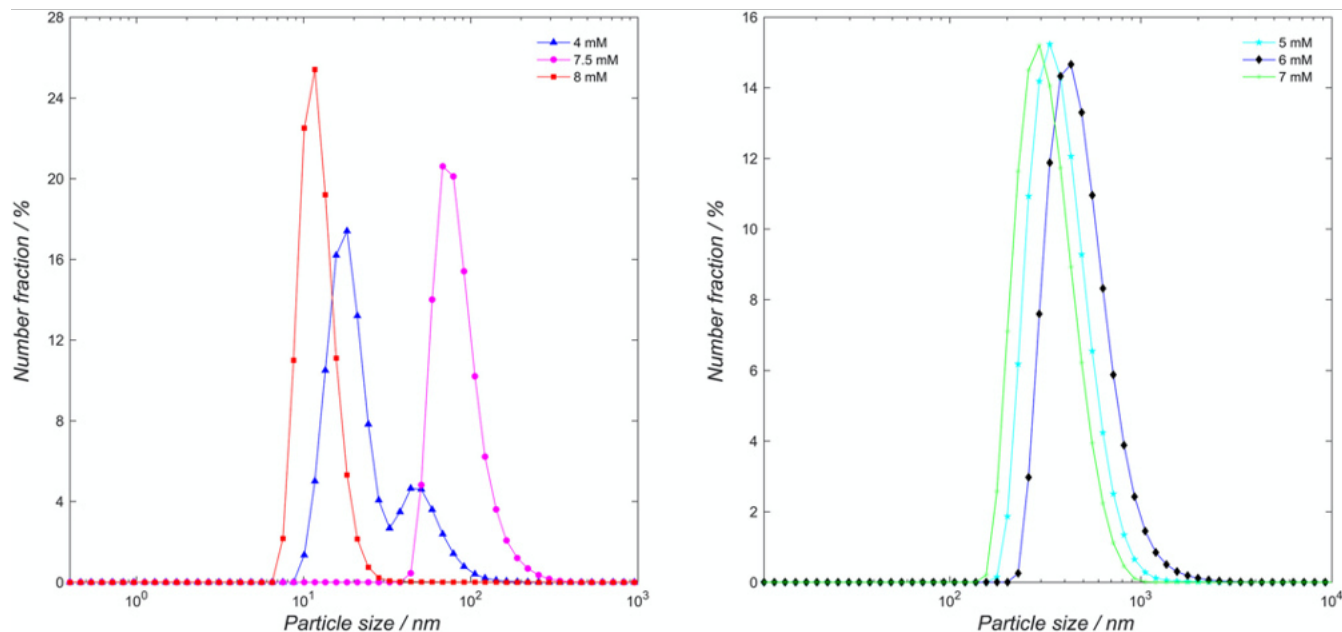


FIGURE 5.5 – Number-based particle size distribution of E100/SDS particles as a function of SDS concentration : DLS (left) and light diffraction (right) measurements.

It can be observed that elaborated complexes mean size increases when increasing surfactant concentration from 4 to 6 mM. At this point, a maximum mean size seems to be reached. A. Akanno et al. [48] pointed out the fact that turbidity increase in the ascendant part of the precipitation domain is most likely linked to the increase in aggregates size. The formation of complexes involves several polymer chains. Thus, the increasing turbidity is not linked to the formation of more charge-compensated complexes in the bulk phase. Turbid dispersions obtained in our experiments associated with non-neutral ZP measurements support otherwise the hypothesis that the turbidity increase is related to kinetically formed aggregates during the preparation process. Working on phase behavior of PDADMAC and sodium *N*-lauroyl-*N*-methyltaurate aggregates, S. Llamas et al. [49] reported the same tendency. They observed an increase in turbidity and apparent hydrodynamic radius when increasing surfactant concentration in a precise range.

For SDS concentration between 7 mM and 8 mM, a decrease of the mean size is observed. This means that for this range, an increase of SDS concentration produces the inverse effect. The resulting system exhibits a slightly bluish appearance at 7.5 and 8 mM. In other words, turbidity is low at low surfactant concentrations, increases and reaches a maximum before decreasing when the surfactant concentration is high. This is consistent with what was observed by other authors for polycations-anionic surfactant bulk phase behavior [41, 50]. Inside the precipitation domain, minimal mean size is associated with the highest and the lowest concentrations. Between them, there is an increase of the mean size following turbidity trend as shown in Figure 5.6.

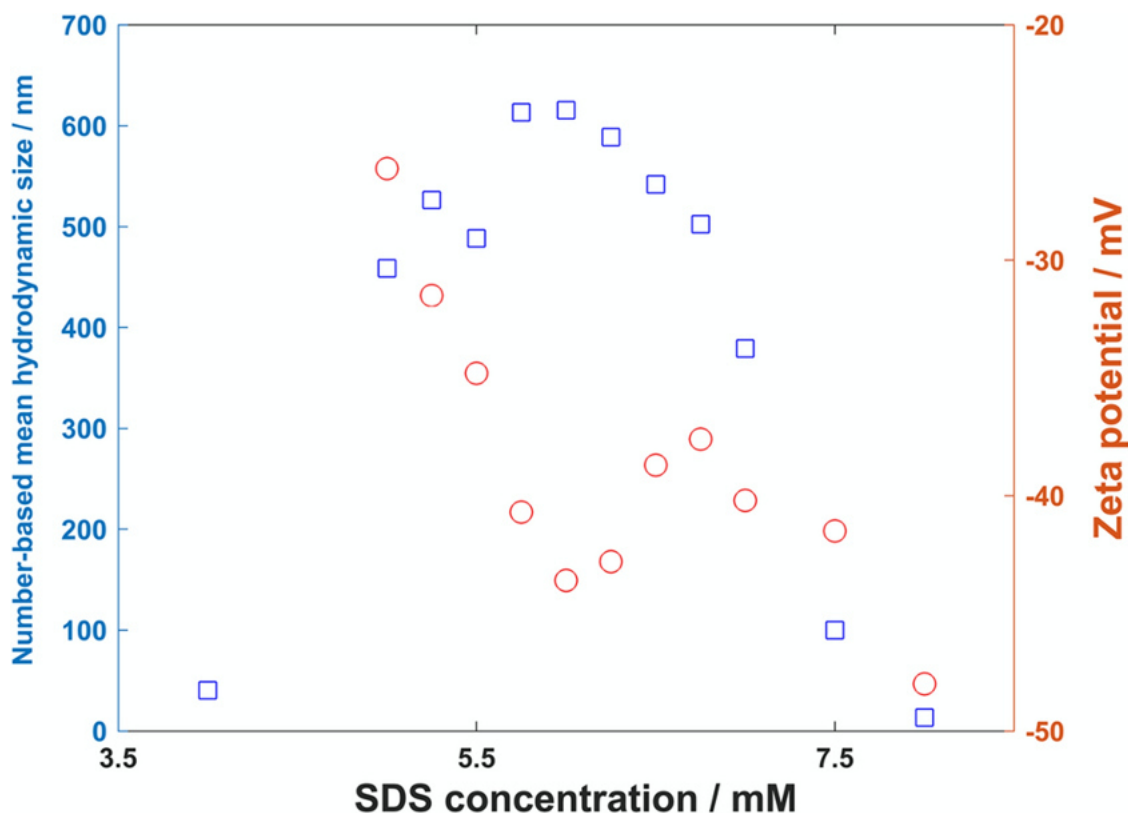


FIGURE 5.6 – Number-based mean hydrodynamic size (squares) and Zeta potential (circles) of Eudragit E100/SDS particles as a function of SDS concentration.

In addition to Eudragit E100/SDS mean particle size, Figure 5.6 presents the evolution

of particles ZP as a function of SDS concentration. The ZP of the obtained dispersions was found to be negative. It reveals the possible restructuration of SDS molecules in the formed aggregates. The zeta potential measured in acidic conditions for the milky dispersions was high enough (in absolute value) to guarantee the aggregates stabilization for at least 24 hours. Sedimentation occurred with an extended storage time. Indeed, zeta potential value ranged from -26 mV at 5 mM to -40.2 mV at 7 mM and pH=3 (Figure 5.6). ZP was not measured as a function of pH since Eudragit E100 is pH-sensitive which affects polymer solubilization and also conformation. Eudragit E100/SDS particles gradually take surfactant charges as its concentration is increased. This is in agreement with what was reported in the literature [30].

The third domain of the phase behavior of Eudragit E100/SDS mixtures is defined for SDS concentration beyond 8 mM. For this concentration range, the system (Eudragit E100/SDS mixtures) was found to be totally non-turbid (see Figure 5.3). When increasing surfactant concentration from neutralization concentration point (CNC) to CMC and further, many authors have observed the non-formation of complexes. This can be attributed to micelles interactions with the oppositely charged polymer inducing good solubilization rather than precipitation via charges screening as discussed above.

5.3.4 Cationic surfactant : CTAB

The effect of CTAB on precipitation of both Eudragit E100 and L100 was investigated as a function of surfactant concentration ranging from 0.1 mM to 20 mM (20 times the CMC value). As expected, no effect of CTAB on cationic Eudragit E100 was observed. This is due to repulsive electrostatic interactions and also to the marginal effect of attractive hydrophobic interactions.

As for Eudragit E100/SDS system, three CTAB concentration domains can also be identified for Eudragit L100/CTAB system. For low concentrations (i.e. below 4.5 mM), the

amount of CTAB is not sufficient to induce any screening effect of oppositely charged chains. By increasing CTAB concentration above 4.5 mM (five times CMC value) at a pH=7, bluish dispersions are obtained. This defined the second CTAB domain (see Figure 5.7).

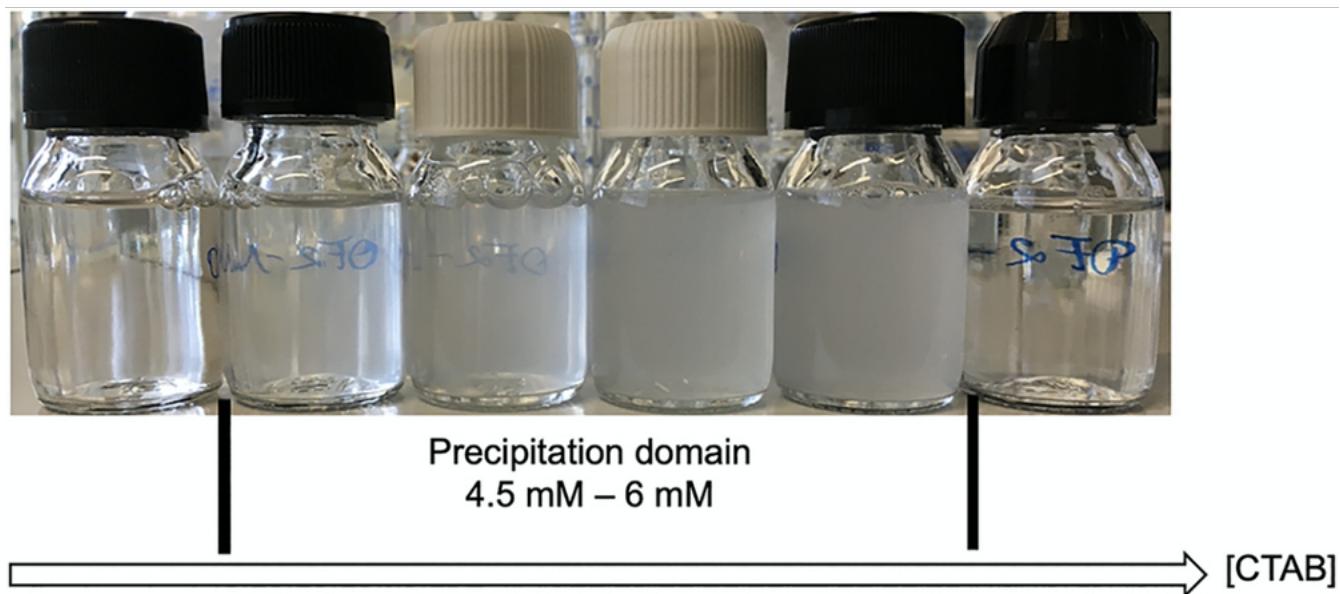


FIGURE 5.7 – Picture showing the three CTAB interactions domains with Eudragit L100. Left : CTAB concentration < 4.5 mM, no screening effect, no precipitation. Middle : complexation and Eudragit L100/CTAB precipitation (4.5-6 mM). Right : Complexes solubilization for high CTAB concentrations (beyond 6 mM).

In fact, by increasing surfactant concentration, increased turbidity is observed. For CTAB concentrations ranging from 5 to 6 mM, milky dispersions are obtained. Based on the explanations given previously, it can be deduced that the cationic charges of CTAB gradually screened Eudragit L100 negative charges. Contrary to Eudragit E100, solubilized Eudragit L100 presents negatively charged pendant groups along his chain [15]. Positive charges brought by the surfactant counterbalance the polymer negative charges and induce phase separation. The phenomenon occurred for polymer to surfactant charge ratio of approximately 2.5 to 3.5 following the micelle-induced precipitation mechanism that is illustrated in Figure 5.8.

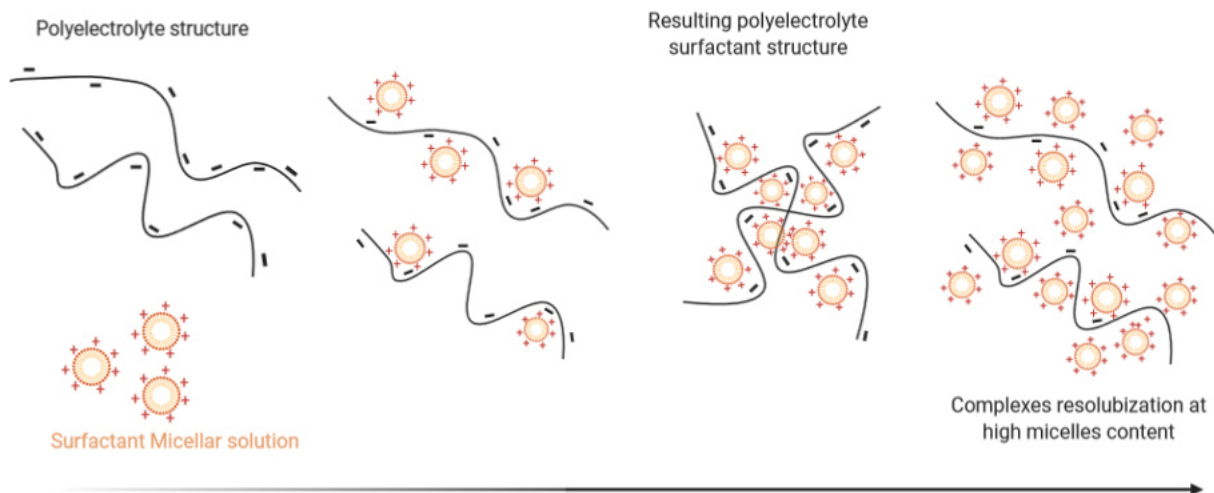


FIGURE 5.8 – A scheme illustrating interactions between negatively charged Eudragit L100 polyelectrolyte chains and positively charged CTAB micelles. (a) CTAB micelles binding to Eudragit L100 chains. (b) Polyelectrolyte chains collapse as Eudragit L100-CTAB complex. (c) Complex resolubilization occurred at high micelles content.

For this precipitation domain, Figure 5.9 presents size distributions with their corresponding mean diameter and zeta potential of Eudragit L100/CTAB particles as a function of CTAB concentration. Contrary to what was observed for the previous Eudragit E100/SDS system, there is no marked effect of surfactant concentration inside the precipitation range on particles size distribution.

Zeta potential increased with increasing CTAB concentration from -26.7 mV at 4.5 mM to $+20$ mV at 6 mM. This increase of ZP is in agreement with what was stated before for Eudragit E100/SDS system.

The third domain is defined for CTAB concentration beyond 6 mM ($\simeq 7$ times CMC value). For this concentration range, the concentration of micelles is sufficient not only to interact with the oppositely charged domains on the polymer chain, but also to enhance the solubility of the forming complexes. In fact, the charges screened by adsorbed CTAB polar parts are replaced by non-involved molecules, leading consequently to more water complexes

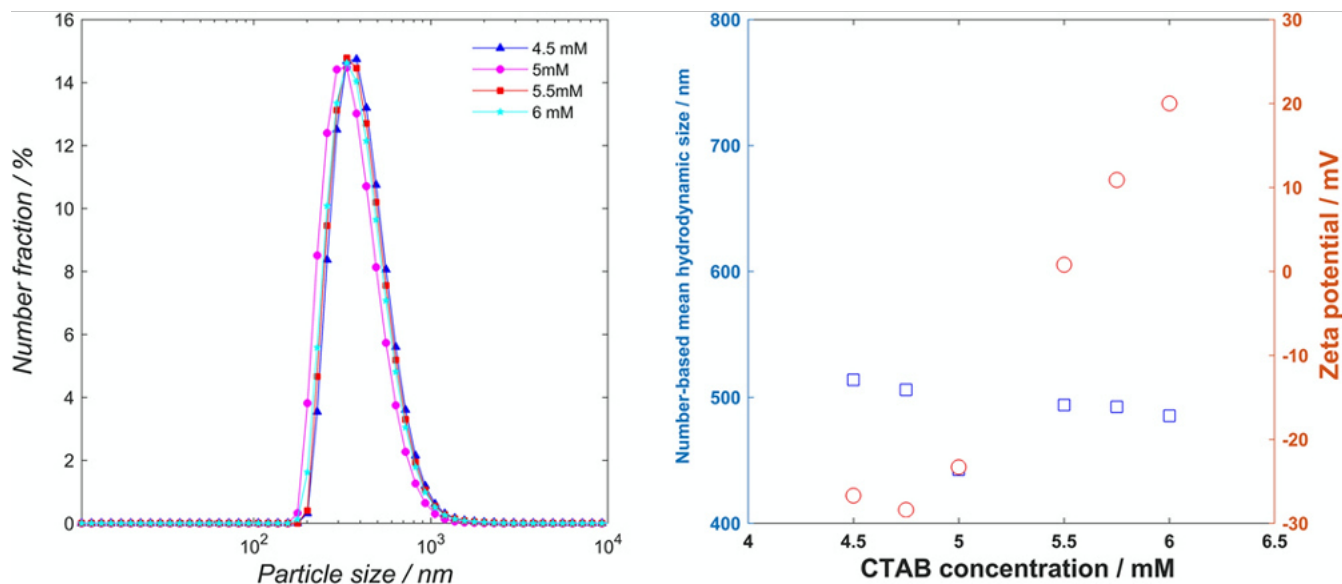


FIGURE 5.9 – Number-based size distribution of L100/CTAB particles as a function of CTAB concentration (left) Number-based mean size (squares) and Zeta potential (circles) of Eudragit L100/CTAB particles as a function of CTAB concentration (right).

[40] (see Figure 5.7).

5.3.5 Effect of pH on the precipitation of oppositely charged Eudragit L100/CTAB and Eudragit E100/SDS

The effect of pH on the bulk phase behavior of oppositely charged systems Eudragit E100/SDS and Eudragit L100/CTAB was also investigated. For this purpose, Eudragit E100 and L100 were solubilized respectively in more acidic and more basic mediums. The same experimental protocol as described before was followed. Surfactant concentration was set to 5 mM and 4.5 mM respectively for SDS and CTAB.

First, the pH (in the investigated range) has no drastic effect on the investigated polyelectrolytes and surfactants.

The effect of pH on E100/SDS system was performed for pH values ranging from 0 to 2.5 and the hydrodynamic particle size was found to increase with decreasing the pH. This

can be mainly attributed to salt effect rather than pH effect. In fact, too acidic pH induces high salinity which is known to affect colloidal stability by inducing aggregation phenomena and consequently large particle size. Another significant observation that is made from this series of experiments is the larger precipitation domain. Precipitation already occurs at SDS concentration of 3 mM. As for example, turbid samples were observed for SDS concentrations ranging from 3 to 15 mM and 3 to 25 mM respectively for experiments performed at pH=1 and 0.

On the other hand, the effect of pH on L100/CTAB was also investigated in the pH range from 7 to 14. The polymer Eudragit L100 is negatively charged in this pH range and totally soluble. The ionic strength increases with increasing the pH and consequently, large particles/aggregates are formed. Such behavior is similar to E100/SDS at acidic pH values as discussed above. Here also, larger precipitation domains were observed. Precipitation occurred for CTAB concentration from 4 to 10 mM for experiments performed at pH=13 and 14 for instance.

5.3.6 Effect of salt on the precipitation of oppositely charged Eudragit L100/CTAB and Eudragit E100/SDS

Effect of NaCl on the bulk phase behavior of oppositely charged Eudragit E100/SDS and Eudragit L100/CTAB systems was also investigated. NaCl concentration ranging from 0 to 1000 mM was studied by simple addition during the mixing process. The experiments were performed at pH values of 2.5 and 7 respectively for Eudragit E100/SDS and Eudragit L100/CTAB systems. Surfactants concentrations that were retained for salt concentration influence investigation were 5 mM for SDS and 4.5 mM for CTAB. As expected, salinity was found to have marked effect.

Regarding Eudragit E100/SDS, for low salinity below 50 mM, no marked effect was ob-

served. In fact, milky like dispersions were obtained with comparable turbidity intensities and the hydrodynamic size was found to be almost the same as reported in Figure 5.10.

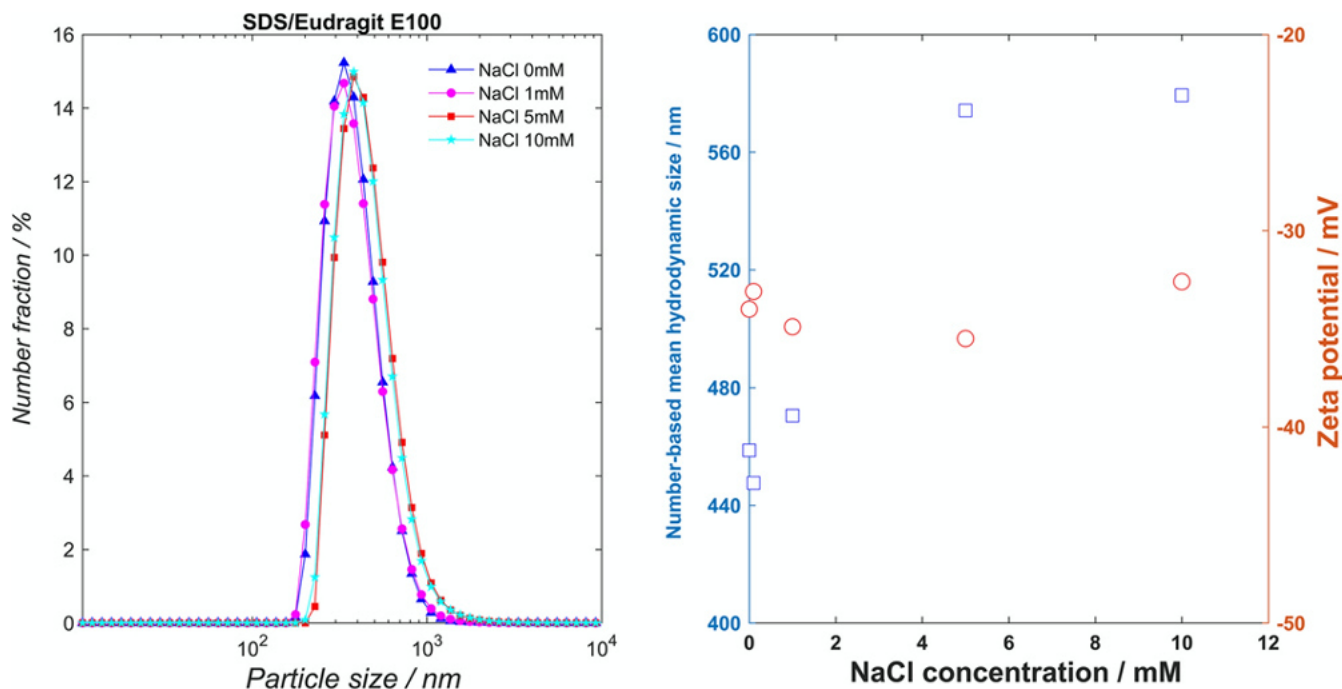


FIGURE 5.10 – Number-based particles size distribution of E100/SDS particles as a function of NaCl concentration, [SDS]=5mM, pH=2.5 (left). Number-based mean size (squares) and Zeta potential (circles) of Eudragit E100/SDS particles as a function of NaCl concentration [SDS]=5mM, pH=2.5 (right).

This can be attributed to negligible salinity effect on attractive electrostatic interactions and in another hand to high surface charge density (i.e. high zeta potential) of the formed particles, revealing good colloidal stability of the obtained dispersion. For high salinity (in the range of 100 to 1000 mM), large particles are obtained demonstrating that ionic strength induces aggregation phenomena of the primary formed particles. Naderi et al. [41] observed that high NaCl concentration induced instabilities in samples prepared by surfactant to polymer mixing method with sediment appearing even under stirring after 1000 hours. Wang et al. [51] also reported similar results for a polycation/SDS system as they observed that NaCl concentration above 0.1 M is helpful to enhance complexes formation. The Figure 5.10 also shows the plot of zeta potential against NaCl concentration. The increase in NaCl concen-

tration does not induce any marked effect on the zeta potential value. This is in agreement with the reported slight increase in particle mean size.

Regarding the Eudragit L100/CTAB system, three domains are observed as a function of NaCl concentration. First, for low ionic strength (0 to 10 mM), similar to E100/SDS, no effect was observed, and the average hydrodynamic size of obtained dispersions is almost in the same range (Figure 5.11).

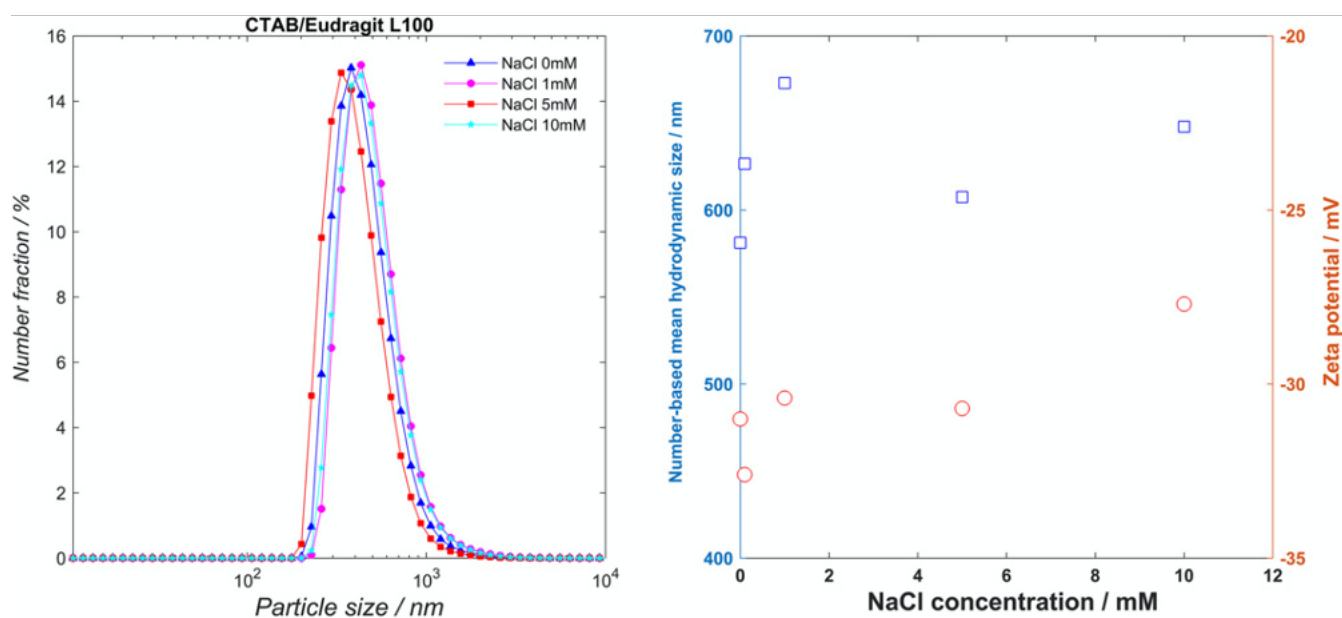


FIGURE 5.11 – Number-based particle size distribution of L100/CTAB particles as a function of NaCl concentration, [CTAB]=4.5 mM ; pH=7 (left). Number-based mean hydrodynamic size (squares) and Zeta potential (circles) of Eudragit L100/CTAB as a function of NaCl concentration, [CTAB]=4.5 mM, pH=7 (right).

However, aggregated dispersions were obtained around 50 mM revealing the instability of the formed particles [41]. Surprisingly, for high salinity (i.e. above 50 mM), no formation of particles was observed. This can be attributed to (i) the screening effect of attractive electrostatic interactions between negatively charged polymer and positively charged surfactant and consequently no particles formation was observed and (ii) the possible reduction of CMC of CTAB surfactant leading consequently to a shift in the precipitation range. K. Pojjażk

et al. [40] reported for polyanionic polymer PSS/CTAB system that the application of high salt concentrations affects the equilibrium phase properties. They observed a considerable decrease of the amount of surfactant bound to the polyelectrolyte. The system tends to be converted as what we observed from a colloidal dispersion to a thermodynamically stable solution of polyelectrolyte and surfactant molecules. They linked this fact to repulsive hydration forces developed between the particles at high ionic strengths.

In brief, the effect of surfactant nature in the presence of Eudragit E100 and L100 polymers was investigated. Non-ionic surfactant Triton X-100 and zwitterionic one SB3-14 have shown no effect when added to polymers. Regarding oppositely charged polymer/surfactant systems, precipitation domains have been pointed out as function of surfactant concentration (Figures 5.4 and 5.8). Submicronic dispersions of Eudragit E100/SDS and Eudragit L100/CTAB were obtained. In the case of Eudragit E100/SDS, it was shown that particle size in the precipitation domain depends on SDS concentration. Regarding the effect of pH and salinity, it was observed that increasing salinity induced an increase of particle size. Surprisingly, for Eudragit L100/CTAB system, no phase separation was observed above NaCl concentration of 50 mM.

5.4 Conclusion

In this study, the effects of surfactant nature and concentration on Eudragit L100 and E100 precipitation were investigated. The results obtained for non-ionic and zwitterionic surfactants are in agreement with those already reported in literature. In fact, these two surfactants do not affect the solubility of both charged polyelectrolytes Eudragit L100 and E100. For non-ionic surfactants, this can be attributed to non-interactions with both polymers. Whereas, for the zwitterionic surfactant, the non-effect was attributed to the non-involved second charge on the surfactant which may enhance the solubilization compared to the in-

volved first charge.

Regarding the effect of charged surfactants on similarly charged polyelectrolytes, no effect has been observed as expected. This has been attributed to the total absence of hydrophobic interactions between alkyl chains of the surfactants and the non-polar segments of the used polyelectrolytes. Whereas, the effect of charged surfactants on oppositely charged polyelectrolytes was found to be more marked. In fact, for both cases Eudragit L100/CTAB and E100/SDS, nanoprecipitation has been observed when the surfactant concentration is sufficient to induce polyelectrolyte charges screening. For high surfactant concentration (i.e. largely higher than the corresponding CMC), the polyelectrolyte/micelles interaction do not induce any precipitation. Despite the partial screening of the charges of the polyelectrolyte, the excess of the charges brought by the micelles induces the solubilization of the formed polymer/micelles complexes.

Conflict of interest

The authors declare no conflict of interest.

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CONCLUSION GENERALE ET PERSPECTIVES

Notre travail avait pour but de caractériser dans un premier temps deux copolymères pH-sensibles : Eudragit E100 et Eudragit L100. Nous nous sommes fixés comme objectif de clairement définir les domaines et conditions de solubilité et de précipitation de ces 2 copolymères. L'objectif était la préparation de particules pH-sensibles d'Eudragit E100 et L100 en solution aqueuse par le procédé de précipitation. Si ces deux copolymères sont utilisés pour l'encapsulation de molécules actives via des procédés tels que la nanoprécipitation, l'évaporation de solvant ou la diffusion de solvant en émulsion double, l'atomisation etc. qui utilisent des solvants organiques, nous avons fait le choix de procéder à cette étude exclusivement en milieu aqueux. C'est aussi en cela que réside l'un des avantages quant à l'utilisation des polymères pH-sensibles en particulier et des matériaux stimulables en général. Ils peuvent permettre en effet de s'affranchir dans une moindre mesure de l'utilisation de solvants organiques pouvant présenter une certaine toxicité pour les applications visées (domaine pharmaceutique par exemple). De plus, l'évaporation des solvants qui suit les procédés de préparation de particules dans lesquels ils sont utilisés engendre un coût supplémentaire. Ainsi, les matériaux stimulables et les polymères pH-sensibles présentent l'avantage de permettre la préparation de particules en agissant sur des paramètres ou stimuli (pH, température, potentiel redox, récepteurs, électricité etc.) et éventuellement de rester en milieu aqueux. Ces matériaux en outre présentent l'avantage lors de leur utilisation d'augmenter l'efficacité (de molécules actives par exemple) et d'améliorer la tolérance du fait de leur spécificité à des conditions (stimuli) bien définies.

Les études expérimentales qui ont été menées ont permis de préparer et de caractériser les particules d'Eudragit E100 et L100 obtenues. La préparation de particules polymériques en solution aqueuse par procédé de précipitation constitue un véritable challenge dans la mesure où il est difficile de les précipiter sans altération de la structure des polymères. Dans un premier temps, la précipitation directe en solution par acidification ou basification de solutions respectivement d'Eudragit L100 et E100 a conduit à des particules de quelques dizaines de

microns ($20\ \mu\text{m}$ et potentiel zêta de $-11\ \text{mV}$ pour les particules d'Eudragit L100, $40\ \mu\text{m}$ et potentiel zêta presque nul à pH neutre pour les particules d'Eudragit E100). La précipitation en milieux tampons a permis d'obtenir des particules submicroniques et nous sommes arrivés à la conclusion que les particules en milieu HCl et NaOH étaient des particules submicroniques agrégées suite à des observations en microscopie. La titration des groupements fonctionnels nous a permis de quantifier les groupements carboxyliques et amines respectivement des Eudragit L100 et E100 responsables de leur solubilisation/précipitation. Ces dosages ont permis d'estimer le taux de groupements amines de l'Eudragit E100 à $4\ \text{mmol/g}$ de copolymère ($8,5\ \text{nmol/mol}$) et celui des fonctions carboxyliques de l'Eudragit L100 à $6\ \text{mmol/g}$ de copolymère ($4,8\ \text{nmol/mol}$). L'étude systématique des conditions de solubilité et de précipitation nous a permis par ailleurs de préciser que pour ces deux copolymères, la solubilité est gouvernée par une action synergique du pH final (ou initial) du milieu, de la concentration en polymère et du temps d'incubation. L'Eudragit L100 est soluble pour des valeurs de pH supérieures à $6,5$ alors que l'Eudragit E100 est soluble lorsque le pH est inférieur à $5,2$.

L'ajout de polymères secondaires durant le procédé de précipitation s'est avérée intéressante car ayant induit des modifications importantes au niveau des particules obtenues en termes de distribution de taille, de potentiel zêta et de stabilité. Ces polymères peuvent en effet jouer dans certains cas le rôle d'agent stabilisant comme le Pluronic ou encore l'alcool polyvinylique. Paradoxalement, en présence d'alcool polyvinylique et du pluronic F68, nous avons observé une augmentation de la taille moyenne des particules. Des particules d'Eudragit L100 de taille moyenne (d_{50}) de $60\ \mu\text{m}$ ont été obtenues pour des rapports massiques polymère secondaire/Eudragit $w=1,33$. Les particules préparées ont présenté un potentiel zêta proche de zéro dû à la réduction de la charge de surface des particules. Des suspensions de particules sphériques d'Eudragit L100, stables (potentiel zêta de $+45\ \text{mV}$), avec une distribution de taille resserrée autour de $200\ \text{nm}$ ont été obtenues en présence du polyéthylèneimine (qui est un polyelectrolyte cationique). Des différents résultats obtenus, nous avons conclu

à la formation de complexes polyélectrolytiques ou polyplexes impliquant les deux polyélectrolytes de charges opposées, l'Eudragit L100 et le polyéthylèneimine. Ces complexes seraient comparables à ceux décrits dans la littérature [1, 2, 3].

Au même titre que l'addition de polyélectrolytes secondaires, nous nous sommes intéressés à la formation de complexes Eudragit-tensioactif. Ainsi, nous avons pu préparer en solution des particules Eudragit E100/SDS et Eudragit L100/CTAB de taille moyenne de quelques dizaines à quelques centaines de nanomètres. La formation de ces complexes est liée à l'attraction électrostatique entre charges opposées et à l'effet d'écrantage de charges qui réduisent la solubilité du polyélectrolyte. S'agissant des complexes Eudragit E100/SDS, des particules de taille allant de 10 nm à 600 nm ont été obtenues en fonction de la concentration en SDS. Le potentiel zêta de ces particules mesuré à pH=3 évolue de -26 à -40 mV pour une concentration en SDS allant de 5 à 7 mM suffisant pour assurer une stabilité colloïdale aux dispersions. Ceci montre que le SDS, tensioactif anionique, participe à la structuration des particules. Pour le second système, des particules Eudragit L100/CTAB de taille moyenne de 500 nm ont été obtenues. Le potentiel zêta de ces particules, mesuré à pH neutre, varie entre -26 et +20 mV pour une concentration en CTAB allant de 4,5 à 6 mM. On peut déduire ici également que le CTAB, tensioactif cationique, rentre dans la structure des particules préparées. Au-delà d'une certaine concentration en tensioactif (8 mM pour les deux tensioactifs), nous avons pu constater que les micelles favorisent la solubilisation des complexes. Il est important de mentionner que les complexes Eudragit E100/SDS se forment pour des concentrations en SDS inférieures (4 à 8 mM correspondant un rapport de charges polymère/tensioactif compris entre 1,25 et 2,5) à la concentration micellaire critique alors que ceux impliquant l'Eudragit L100 et le CTAB ne se forment qu'en régime micellaire (4,5 à 8 mM de CTAB, rapport de charges polymère/tensioactif allant de 2,5 à 3,5). Dans ce travail, nous avons étudié un nouveau système constitué par les Eudragit et des tensioactifs. Ces systèmes ont été étudiés pour les différentes applications pour lesquelles ils peuvent être intéressants. Les interactions

entre les polyélectrolytes et les tensioactifs de charges opposées sont sensibles à une variété de paramètres, tels que le pH, la force ionique, la procédure et l'ordre de mélange, la densité de charge, etc. Ces paramètres peuvent être utilisés pour contrôler la concentration à laquelle les structures se forment ainsi que le type de structure.

Les différents travaux réalisés nous ont permis de fixer des conditions expérimentales pour la préparation des particules d'Eudragit E100 et d'Eudragit L100 par le procédé de précipitation en solution. La stabilité de ces particules passe par la formation de complexes polyélectrolytiques ou de complexes Eudragit-tensioactif. Ainsi, des nanoparticules ont pu être produites sous certaines conditions expérimentales. Ces nanoparticules pourraient présenter des applications potentielles notamment dans l'industrie pharmaceutique ou cosmétique. Dans l'industrie pharmaceutique, les principes actifs formulés sous forme de nanoparticules ont montré une meilleure biodisponibilité et l'atteinte d'organes cibles difficile à atteindre avec les formulations classiques [4, 5]. Des avancées ont été réalisées au fil des années sur le plan de leur élaboration, leur stabilité mais aussi de leur toxicité. Il serait ainsi intéressant d'étudier l'efficacité d'encapsulation de molécules actives des différents systèmes élaborés au cours de nos travaux et leur aptitude comme vecteurs thérapeutiques. Dans ce sens, nous avons entrepris d'ores et déjà des études d'encapsulation et de relargage d'indicateurs colorés de pH pouvant mimer le comportement de molécules actives. Le choix des indicateurs colorés repose sur la sensibilité aux pH des deux copolymères étudiés. Dans l'élaboration de nanoparticules polymériques comme vecteurs thérapeutiques, des procédés tels que la précipitation, la diffusion en émulsion, l'évaporation d'émulsion simple ou d'émulsion double, l'atomisation sont couramment employés [6]. Bien qu'utilisant des solvants organiques, ces méthodes présentent l'avantage d'être faciles à mettre en œuvre. Une autre méthode faisant appel à des solvants organiques est l'élaboration de nanoparticules via le mélange de deux microémulsions. Cette dernière a montré sa capacité à produire des nanoparticules monodisperses. En effet, ces microémulsions inverses peuvent se comporter comme des nanoréacteurs conduisant à des

particules de seulement quelques dizaines de nanomètres en taille [7, 8, 9, 10, 11, 12, 13, 14]. Ces systèmes ont été utilisés notamment pour la synthèse de nanoparticules de polysaccharides et de protéines par réaction de réticulation [15, 16, 17]. Si les gouttelettes dispersées des microémulsions sont utilisés comme site de polymérisation [18, 19], l'utilisation du procédé de mélange de deux microémulsions dans la synthèse de nanoparticules polymériques n'a à ce jour pas été reportée dans la littérature. Il serait ainsi intéressant de voir le potentiel d'un tel procédé dans l'élaboration de nanoparticules d'Eudragit E100 et L100 partant des résultats obtenus en solution. Il faut mentionner sur ce point précis que nous avons entrepris, là également, des études d'élaboration de particules d'Eudragit E100 et L100 en microémulsions inverses avec comme phases organiques l'octane et le cyclohexane et comme tensioactif du bis (2-ethylhexyl) sulfosuccinate de sodium (AOT). Les expérimentations menées se sont avérées non concluantes. Il sera nécessaire à ce stade d'avoir une meilleure compréhension des microémulsions et de leur dynamique. La finalité serait de pouvoir produire ces particules au sein des nanoréacteurs des microémulsions, étudier et comparer leur efficacité comme vecteurs thérapeutiques avec les nanoparticules produites dans notre étude en milieu aqueux.

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Titre : Polymères pH-sensibles ; Caractérisation et précipitation en milieu aqueux

Résumé : Dans l'industrie pharmaceutique, de nombreux polymères sont employés pour l'encapsulation de molécules actives. Le choix des polymères est fonction de leurs caractéristiques et des applications visées pour les produits élaborés. Parmi les polymères utilisés, on retrouve les copolymères d'acide méthacrylique et leurs esters connus sous le nom d'Eudragit®. Les Eudragit sensibles au pH sont utilisés dans diverses formulations à des fins d'enrobage, de revêtement entérique, de masquage de goût, ou comme vecteurs thérapeutiques de principes actifs pharmaceutiques pour l'amélioration de la perméation à la peau, aux villosités intestinales ou encore à la cornée. Les Eudragit E100 et L100 notamment ont été étudiés de manière approfondie pour leur caractère hydrophile/hydrophobe en fonction du pH et de la salinité pour l'enrobage. Toutefois, la possibilité de préparer des particules sensibles au pH à partir de ces polymères n'a pas été systématiquement explorée en raison de la difficulté résidant dans leur précipitation sous forme de (nano)particules. Ainsi, ce travail de recherche a pour objectif de conduire une caractérisation physico-chimique complète et d'étudier différentes voies de préparation de (nano)particules d'Eudragit E100 et L100 en solution aqueuse par précipitation. Dans la première partie de notre étude, nous nous sommes attelés à clarifier les domaines de solubilité et de précipitation des deux copolymères. Nous avons pu observer que la concentration en polymère, le pH final du milieu ainsi que le temps d'incubation influencent la solubilité des Eudragit E100 et L100. La titration des 2 copolymères nous a permis de doser les fonctions carboxylates de l'Eudragit L100 et amines de l'Eudragit E100. De plus, l'impact de divers paramètres tels que le pH, la concentration en polymère et la force ionique du milieu sur la précipitation a été étudiée. Dans une seconde partie, l'influence de divers polymères secondaires sur la complexation et les propriétés colloïdales des particules d'Eudragit E100 et L100 a été étudiée. Dans ce cadre, le polyéthylèneimine a montré sa capacité à complexer l'Eudragit L100 donnant des dispersions stables et des tailles de particules submicrométriques. Dans un troisième temps, l'effet des tensioactifs sur la précipitation des deux polymères a été étudié. Ceci nous a permis d'identifier la nature des interactions impliquées et le mécanisme de complexation des deux Eudragit E100 et L100 en fonction de la concentration en tensioactif.

Mots clés : Eudragit, Précipitation, Polymères pH-sensibles, Polyplexes, Complexes Polyelectrolyte- Tensioactifs.

Title : pH-responsive polymers ; Characterization and precipitation in aqueous medium

Abstract : In pharmaceutical industry, many polymers are used for the encapsulation of active ingredients. Polymers' choice depends on their characteristics and the intended applications of the developed products. Among the commonly used polymers, methacrylic acid and their ester copolymers known as Eudragit® ; pH-sensitive polymers have been used for years in various formulations for coating, enteric coating, taste masking, or as therapeutic vehicles. Studies have shown that Eudragit improves the permeation of pharmaceutical active ingredients through skin, intestinal villi or cornea. Eudragit E100 and L100 in particular have been extensively studied for their ability of swelling/deswelling as a function of pH and salinity for coating. However, the possibility of preparing pH-sensitive particles from these polymers has not been systematically explored due to the difficulty of precipitating them as (nano)particles. Thus, the aim of this research work is to fully characterize these two Eudragit polymers and to study different ways of preparing Eudragit E100 and L100 (nano)particles in aqueous solution by precipitation process. In the first part of this work, we brought some clarifications on the solubility and precipitation domains of the two copolymers. We observed that a synergic action of the polymer concentration, the final pH of the medium as well as the incubation time influence the solubility of Eudragit E100 and L100 which is neglected in the state of the art. The titration of the two copolymers allowed us to determine the carboxylate and the amino content of respectively Eudragit L100 and Eudragit E100. In addition, the influence of various parameters such as pH, polymer content and ionic strength of the medium on both Eudragit precipitation was studied. In a second part, the influence of various secondary polymers on complexation and on the colloidal properties of Eudragit L100 and E100 particles was investigated. In this context, polyethylenimine was found to form a complex with Eudragit L100 and to stabilize the formed particles exhibiting submicrometric size with a narrow size distribution and high stability. In a third step, surfactants effect on the precipitation of Eudragit E100 and E100 was studied. This allowed us to identify the nature of polymer-surfactant interactions and the complexation mechanism of Eudragit E100 and Eudragit L100 as function of surfactant concentration.

Keywords : Eudragit, Precipitation, pH-sensitive polymers, Polyelectrolyte complexes (PECs), polyelectrolyte-surfactant complexes (PESCs).