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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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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.

0.1 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.

0.2 Materials and methods

0.2.1 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 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).

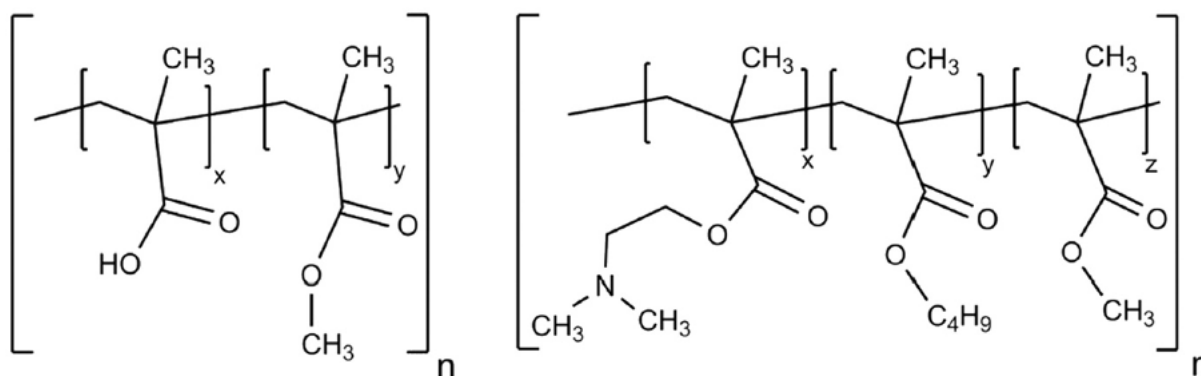


FIGURE 1 – Molecular structures of methacrylic acid - methyl methacrylate copolymer (1 :1) EUDRAGIT[®] L100 (left) and dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate tri-copolymer (2 :1 :1) EUDRAGIT[®] E100 (right) from Evonik Röhm GmbH (Germany).

0.2.2 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.

0.3 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.

0.3.1 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 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. 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, 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

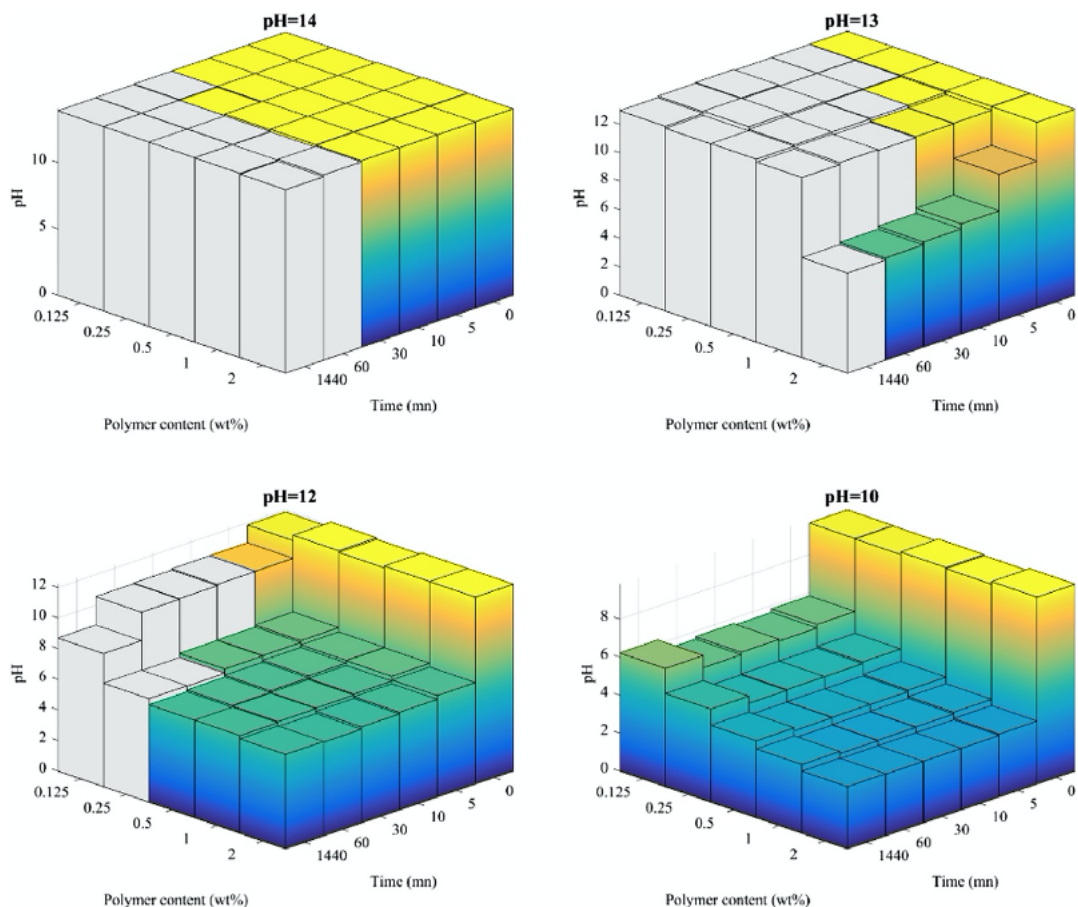


FIGURE 2 – Solubilization of Eudragit L100 in NaOH medium as a function of polymer amount and time. The grey bars refer to the solubilized samples whereas the other samples remain insoluble.

the two investigated polymers are closely related to the polymer content and its incubation time as shown in figures 2 and 3.

0.3.2 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 1). As expected, the effect of the polymer on the initial pH is less marked compared

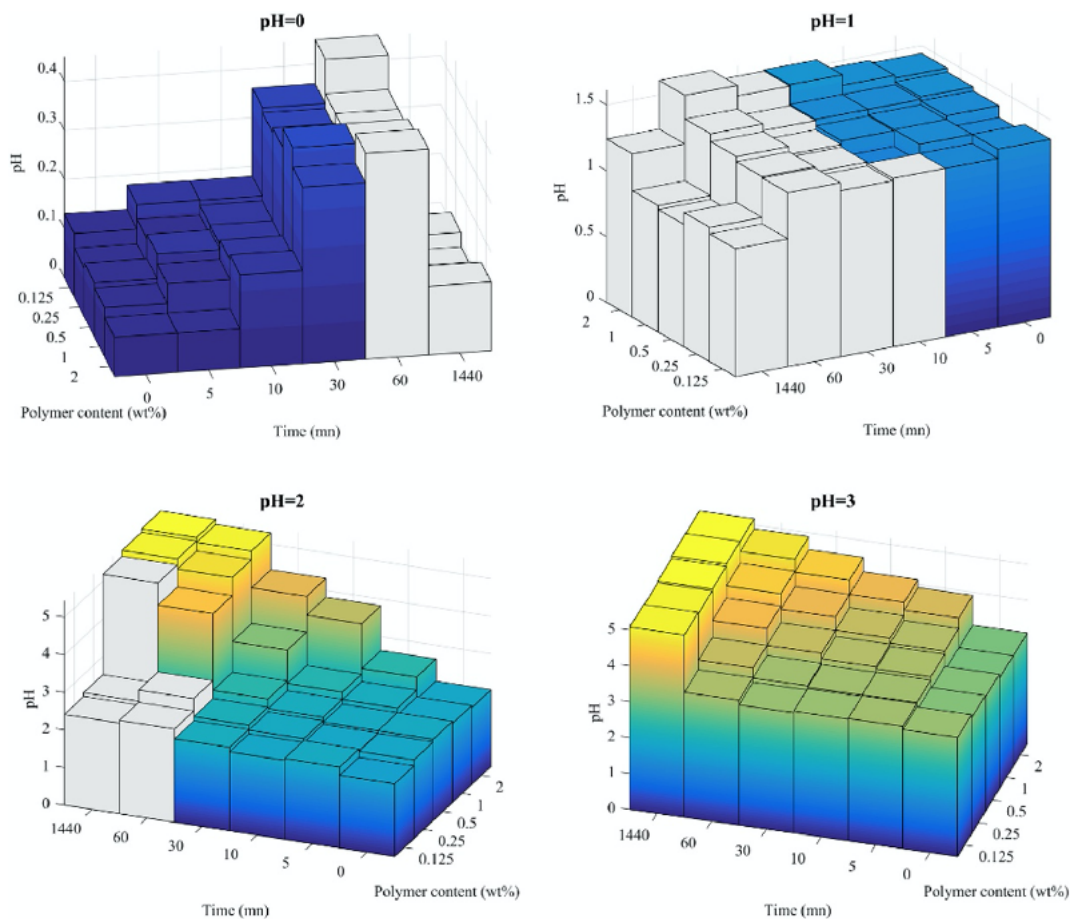


FIGURE 3 – Solubilization of Eudragit E100 in HCl medium as a function of polymer amount and time. The grey bars refer to the solubilized samples whereas the other samples remain insoluble.

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 pH=6.50 and Eudragit E100 up to 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 [$\text{HPO}_4^{2-} : \text{H}_2\text{PO}_4^-$]	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 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.

0.3.3 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 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 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).

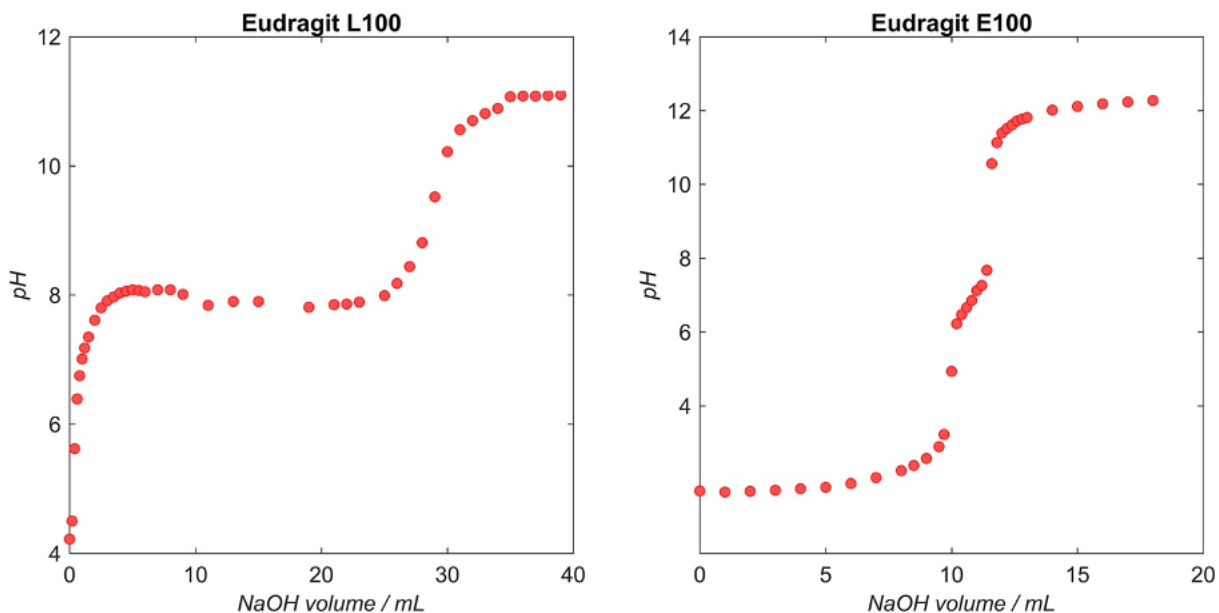


FIGURE 4 – pH titration of Eudragit L100 0.5 wt.% with NaOH 10^{-2} M solution (left) and Eudragit E100 0.5 wt.% solubilized in HCl 1 M with NaOH 10^{-1} M solution (right).

0.3.4 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 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 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.

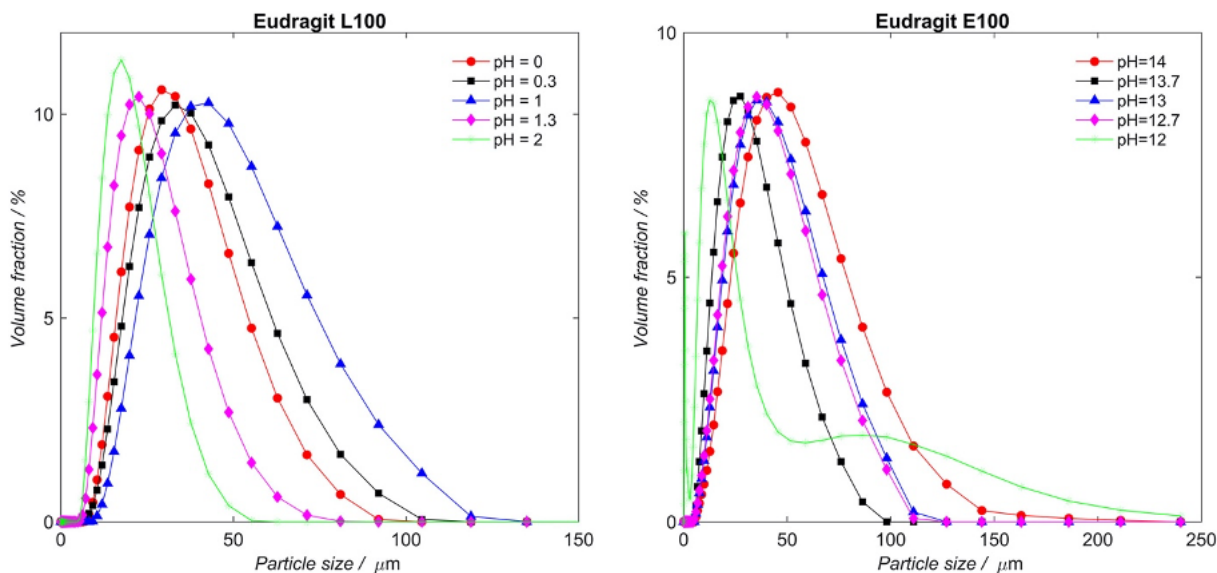


FIGURE 5 – Volume-based size distribution of precipitated Eudragit L100 (left) and Eudragit E100 (right) as a function of precipitating pH.

0.3.5 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 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.

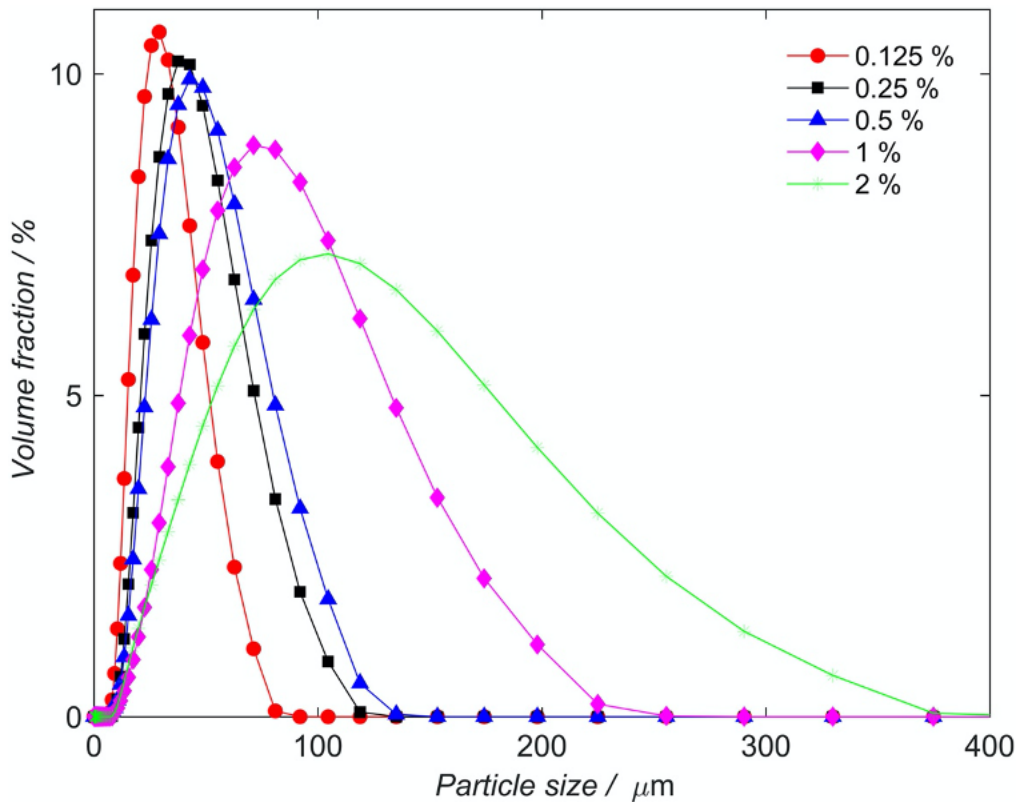


FIGURE 6 – Volume-based Eudragit L100 particle size distributions at different initial polymer concentrations.

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. 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.

0.3.6 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 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 7) and TEM analysis (Figure 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 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 2 – Precipitation of Eudragit L100 and Eudragit E100 20 wt.% with 1M HCl and 1M NaOH respectively.

0.3.7 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 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.

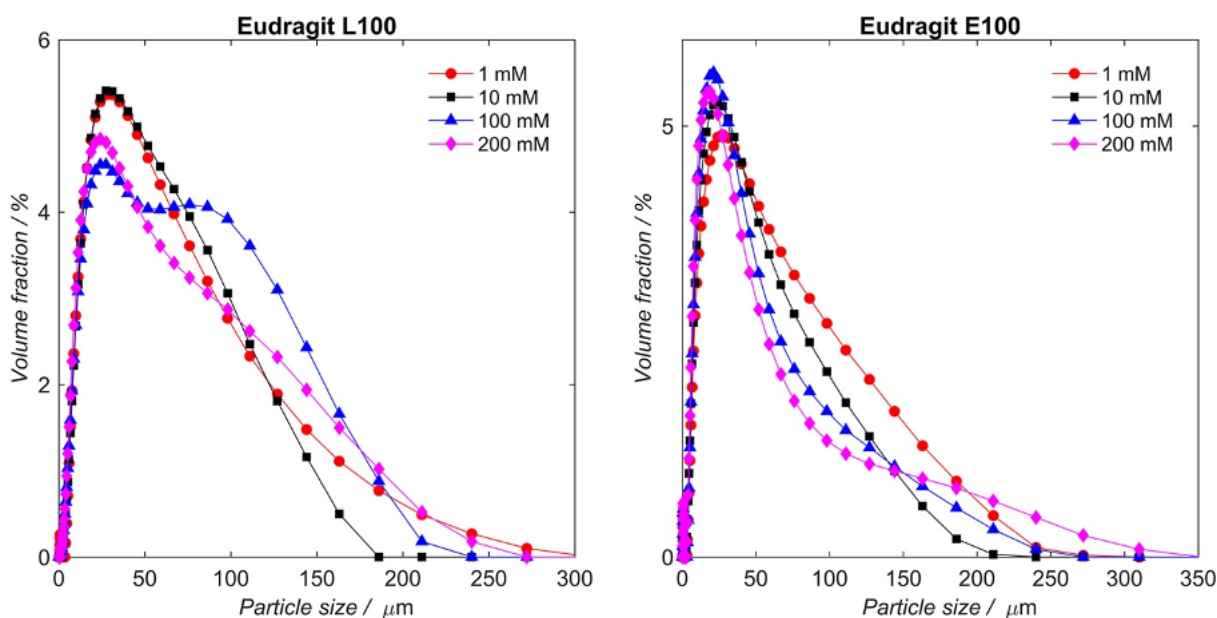


FIGURE 7 – Eudragit L100 (left) and Eudragit E100 (right) particle size distribution as a function of phosphate buffer concentration.

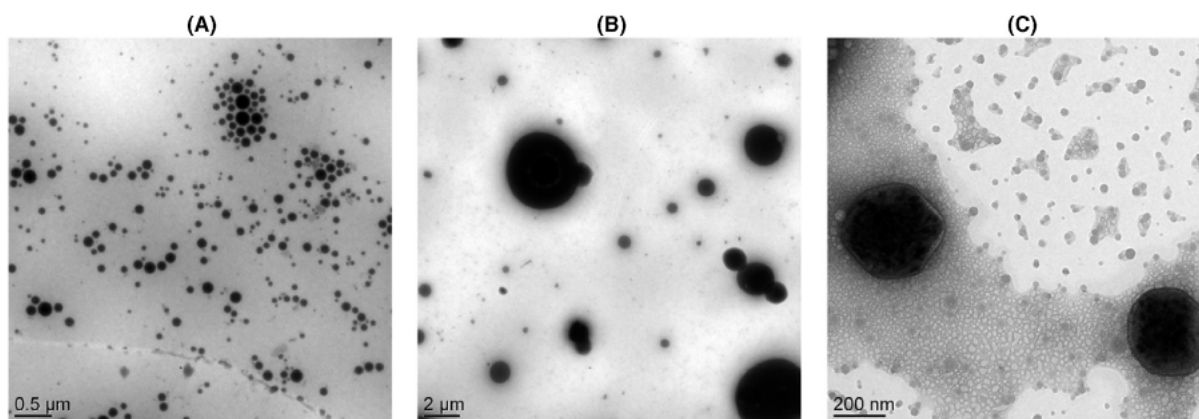


FIGURE 8 – Electronic microscopic pictures of 100 mM buffer Eudragit L100 (a), 10 mM buffer Eudragit E100 (b) and 200 mM buffer Eudragit E100 (c).

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.

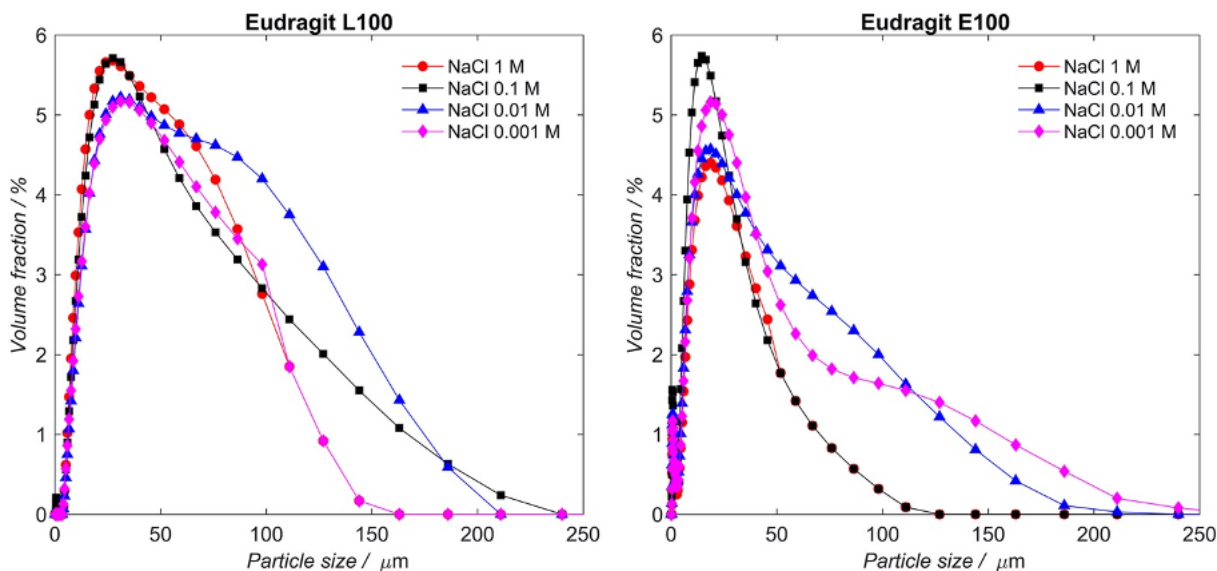


FIGURE 9 – Number-based particle size distribution of Eudragit L100 (left) and Eudragit E100 (right) as a function of NaCl concentration.

0.3.8 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.

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 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 – Equivalent volume addition of Eudragit L100 and E100.

0.4 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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