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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.

0.1 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.

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). 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, Mw=25000 g/mol, Mn~10000) was purchased from Aldrich Chemistry (Germany), polyvinyl alcohol (Mw=200000 g/mol) from Merck KGaA (Darmstadt, Germany) and polyacrylic acid 40% wt. (Mw=30000 g/mol) from Aldrich Chemical Company (Milwaukee, USA). Dextran 40 (Mw=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 1).

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

TABLE 1 – Molecular structures of Eudragit L100, E100 and studied secondary polymers.

0.2.2 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.

0.3 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.

0.3.1 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].

0.3.2 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 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.

0.3.3 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.

0.3.4 Influence of polyvinyl alcohol

Figure 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 μm , whereas without PVA this mean size is around 20 μm . 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.

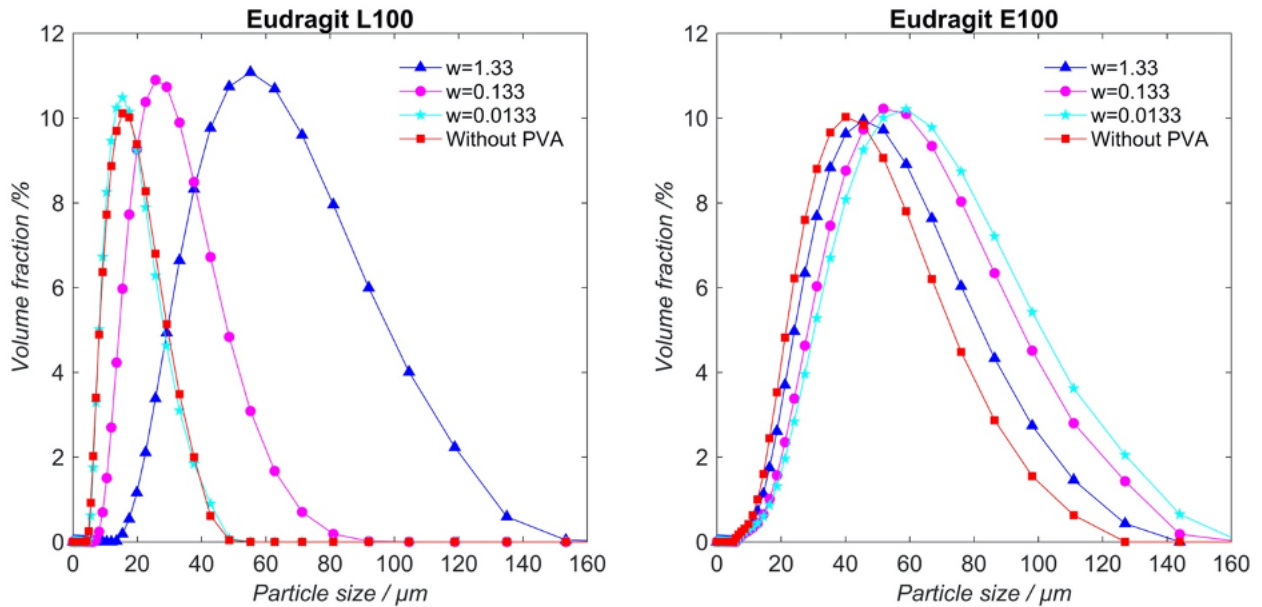


FIGURE 1 – Volume-based hydrodynamic particle size distribution of particles formed in presence of PVA as a function of w ratio.

0.3.5 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 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.

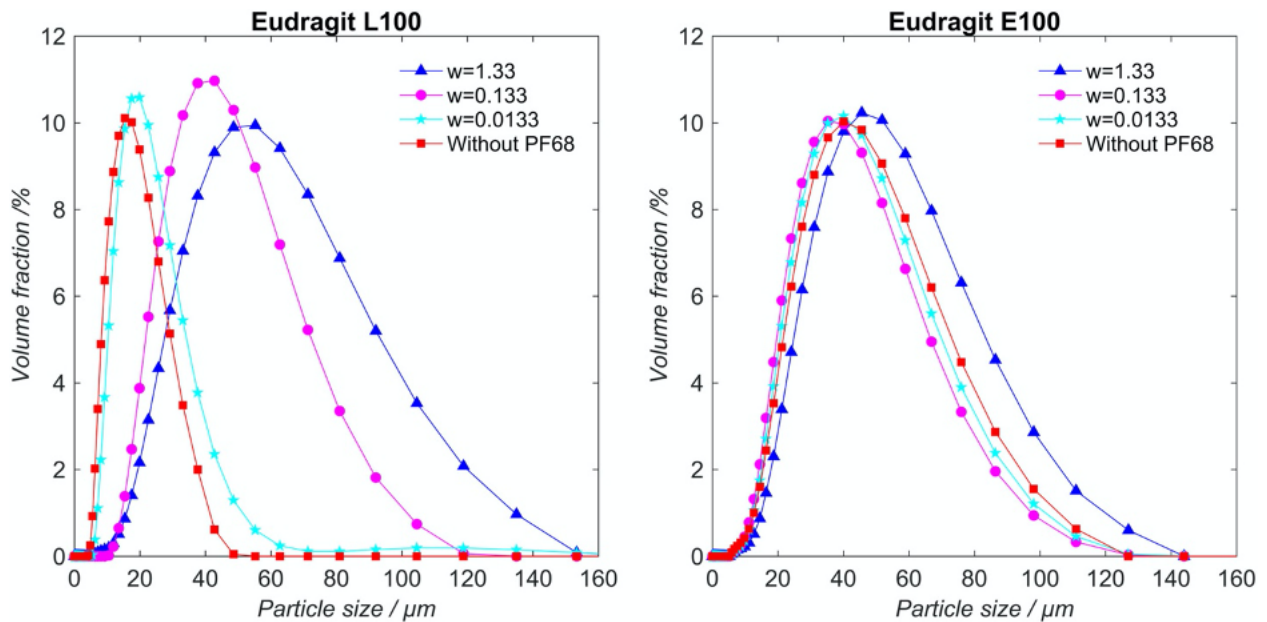


FIGURE 2 – Volume-based hydrodynamic particle size distribution of particle formed in presence of Pluronic PF68 as a function of w ratio.

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].

0.3.6 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 2. As it can be noticed from Figure 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) 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 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 5.

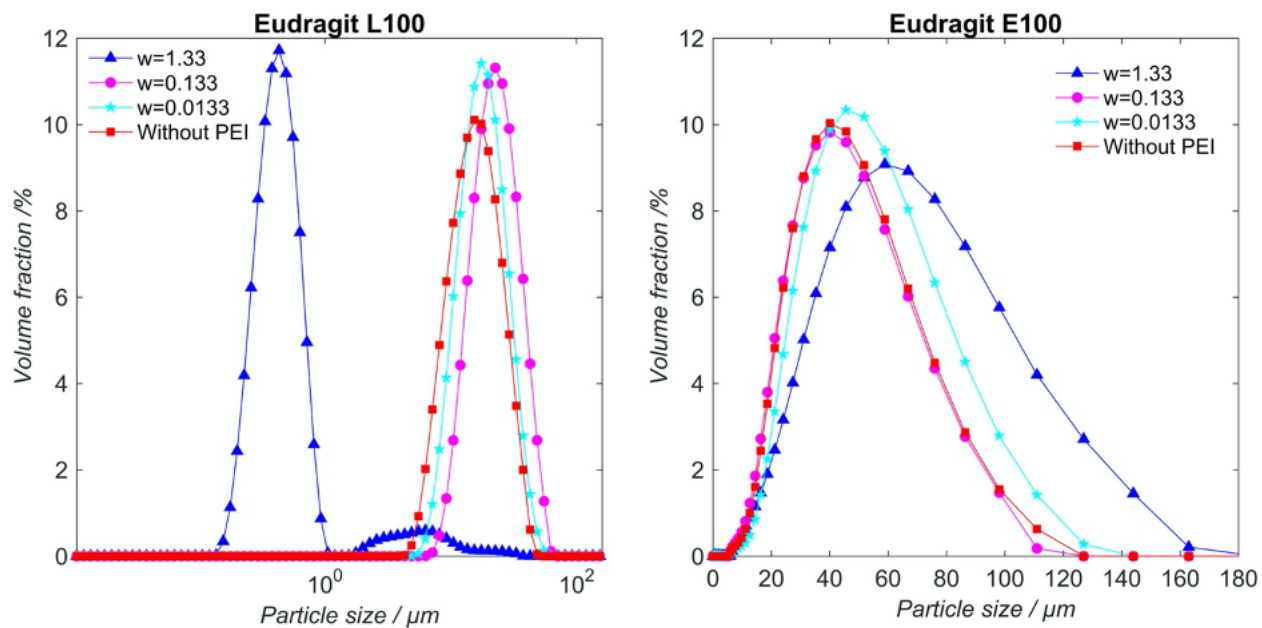


FIGURE 3 – Volume-based hydrodynamic particle size distribution of particle formed in presence of polyethylenimine (PEI) as a function of w ratio.

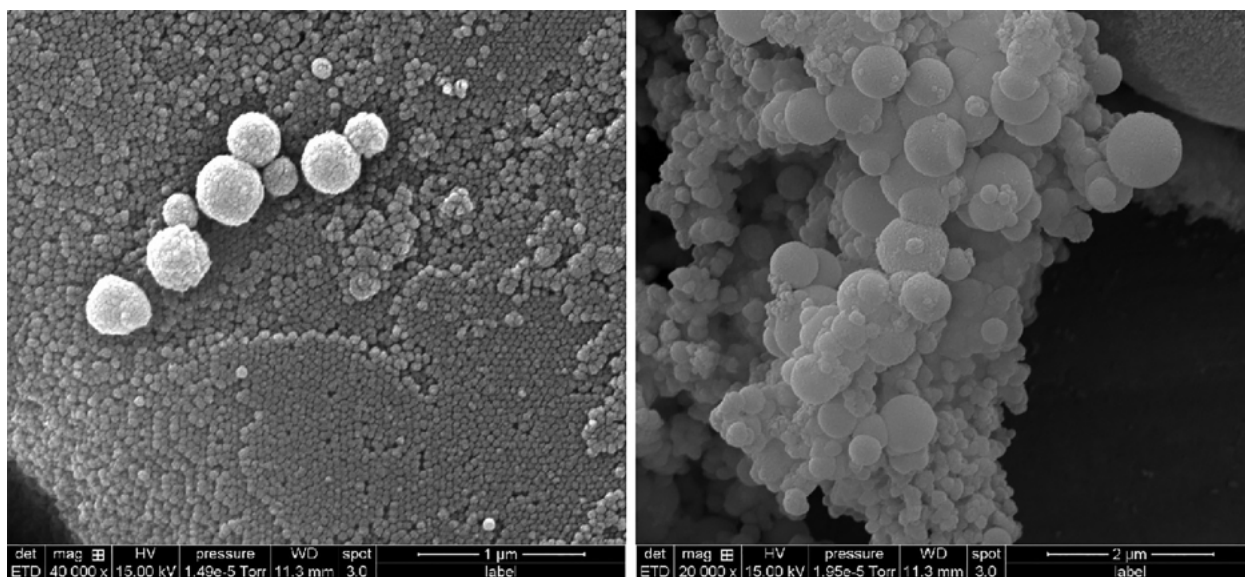


FIGURE 4 – SEM images of precipitated Eudragit particles in presence of polyethylenimine for $w=1.33$

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

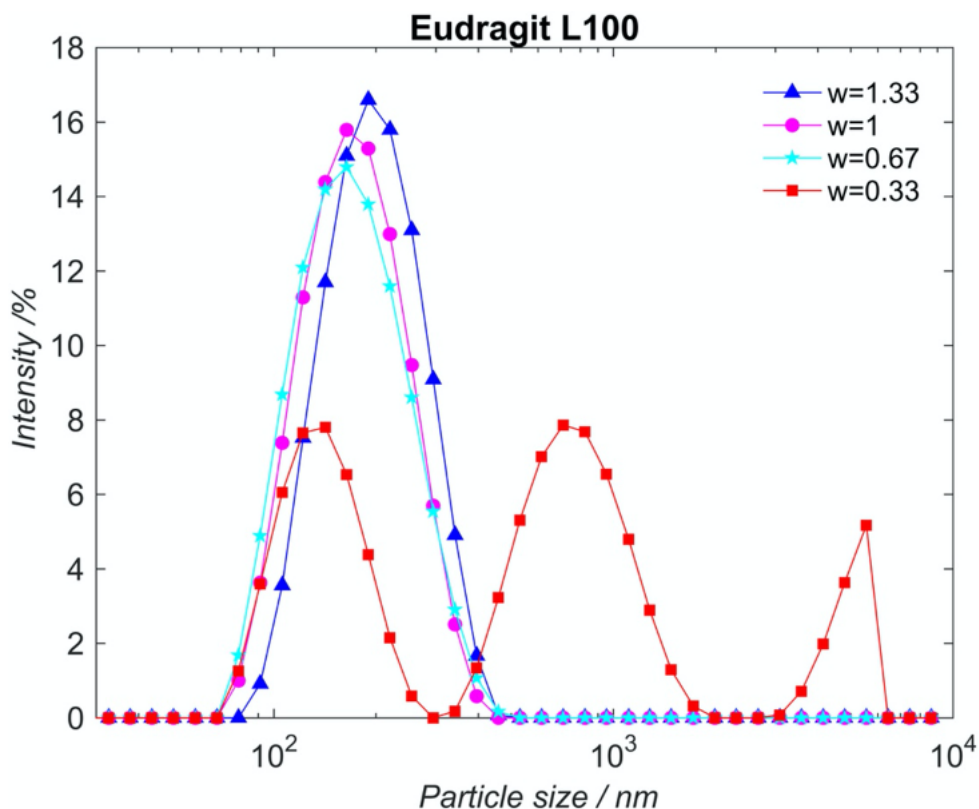


FIGURE 5 – SEM images of precipitated Eudragit particles in presence of polyethylenimine for $w=1.33$

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.

0.3.7 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.

0.4 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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