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Research paper

Spray-drying enteric polymers from aqueous solutions: A novel, economic, and environmentally friendly approach to produce pH-responsive microparticles

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ABSTRACT

We describe a novel method to fabricate pH-responsive microparticles suitable for oral delivery using an aqueous-based spray-drying approach. The approach involves the neutralization and generation of water-soluble salt forms of enteric polymers. The methacrylic acid polymers (Eudragit L and Eudragit S) were added separately to aqueous solutions of ammonium hydrogen carbonate; the solutions were then spray-dried. FTIR analysis of the harvested microparticle products identified the presence of ammonium methacrylate with the appearance of a peak at 1550 cm^{-1} corresponding to the stretching of the N–H bond. Incubating the microparticles for three hours at 70 °C and 130 °C for the Eudragit S and L products, respectively, was sufficient to eradicate the ammonium residues. The microparticles, loaded with the model drug prednisolone, were spherical and small in size (2–5 μm). Moreover, the particles were gastro-resistant, and release was rapid and complete at small intestinal conditions. The pH threshold of release of the Eudragit S and Eudragit L microparticles was lowered from 7 and 6 to 6.5 and 5.5, respectively. In bicarbonate media, which are physiological and representative of the conditions of the proximal small intestine (mHanks) and the distal small intestine (Kreb's), drug release from these spray-dried microparticles was faster compared to microparticles produced from conventional emulsion solvent evaporation methods. This new microparticle preparation concept obviates the need for organic solvents and utilizes spray-drying techniques that are amenable to industrial application; the approach therefore offers economic, safety, and environmental benefits.

1. Introduction

Spray-drying is a one-step production method that is scalable to industrial levels [1], with the possibility of avoiding the use of organic solvents [2]. It has several advantages including high reliability, reproducibility, and control of particle size [3]. The method is commonly used in the food and pharmaceutical industries particularly to produce small size particles of poorly soluble drugs, either alone or mixed with hydrophilic fillers [4–7]. These advantages make spray drying a very attractive approach to produce microparticles. However, attempts to produce enteric microparticles via this method have been unsuccessful [8–13].

Alternative preparation methods for the fabrication of microparticles have included emulsion solvent evaporation [14–19] and coacervation [20,21]. However, these preparation methods suffer major shortcomings, including the presence of solvent residues in the finished product [22], the difficulty in preparing small size microspheres from coacervation [23], the complication of scale-up, and the need for relatively large quantities of organic solvents in the case of emulsion solvent evaporation [23,24].

A variety of formulation strategies have been implemented in an attempt to fabricate pH-responsive microparticles using spray-drying technology. For instance, an organic solution of drug and polymer were spray dried to prepare enteric microparticles [12]. Despite the acidic nature of the model drug (ketoprofen), poor control of drug release was reported at low pH. An alternative approach involved spray-drying an aqueous drug solution containing suspended enteric polymer particles [11]. However, the size of the microparticles was inconsistent, and the particles did not show pH-dependent drug release, highlighting the importance of incorporating the drug into the polymeric matrix of the microparticle to achieve efficient control of drug release in acid.

In general, the methods used to manufacture enteric microparticles require the need for sizable quantities of organic solvents. Due to the toxic inflammable nature of these solvents, there is an increasing trend to shift toward aqueous-based formulations [25–27]. Several aqueous enteric coating systems suitable for application to conventional dosage forms (tablets, pellets, or granules) are now available. However, there has been little work

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to develop aqueous-based preparation approaches for pH-responsive microparticles. This is probably due to the poor solubility of both the drug molecules and the enteric polymers in water.

It is of environmental and economic interest to develop a technology that combines the advantages of aqueous polymeric solutions and spray-drying technology. With this in mind, alkaline solutions, such as sodium hydroxide, have been employed to neutralize the acidic groups in enteric polymers and generate soluble salt forms in solution suitable for spray-drying [8,9]. However, the microparticles prepared by these methods suffered from major shortcomings including poor morphology and poor control of drug release in acid [8,9]. In this work, we describe a novel and efficient approach to manufacture enteric microparticles by spray-drying aqueous polymer solutions.

2. Materials and methods

2.1. Material

Prednisolone was purchased from Sanofi-Aventis (Romainville, France). Sorbitan sesquioleate, ammonium hydrogen carbonate, and liquid paraffin were purchased from Sigma Aldrich, (Poole, UK). Glycerol monostearate (GMS, Imwitor 900) was obtained from Huls AG (Witten, Germany). Polymethacrylate polymers: Eudragit S, Eudragit L were provided by Evonik Degussa Chemicals (Darmstadt, Germany).

2.2. Methods

2.2.1. Development of microparticles by spray-drying aqueous polymer solutions

Eudragit S was chosen as the model polymer. To optimize the manufacture of the Eudragit S microparticles a variety of parameters were investigated including, polymer solution concentration, the inlet and outlet temperatures in the spray dryer, and the addition of surfactant and glycerol monostearate (GMS) (Formulations F1–F6) (Table 1). The optimized microparticle manufacture procedure (F6) is detailed as follows (Fig. 1): Initially, 8 g of Eudragit S was added to an aqueous solution of 0.96% w/v ammonium hydrogen carbonate (pH 8.5). Prednisolone (266 mg) was dissolved in 15 ml of ethanol, which was then added under stirring to the aqueous solution. In order to improve the morphology and hydrophobicity of the microparticles 0.4 g of sorbitan sesquioleate and 0.4 g of glycerol monostearate (dissolved in 10 ml hot ethanol) were added to the above solution while stirring at 65 °C. The total volume was made up to 400 ml with distilled water. The solution was subsequently spray-dried using a Niro SD Micro spray dryer (GEA Pharma systems Inc., Switzerland) with an inlet temperature of 90 °C, outlet temperature of 48 °C, and a feed rate of 18% (out of a maximum 5 L/h).

With all six formulations, the following parameters remained constant: air flow rate 600 L/h, atomizer flow rate: 2.5 kg/h, chamber flow rate: 25/2.5 kg/h, and nozzle pressure: 1.5 bar.

This optimized method (F6) was also used as a basis to fabricate microparticles with Eudragit L. An aqueous solution of the enteric polymer was prepared by dissolving Eudragit L (8 g) in a lower concentration (0.625% w/v) of ammonium hydrogen carbonate (pH 8.5). The preparation procedures were conducted as above. The spray-drying inlet temperature was set at 90 °C; the outlet temperature was recorded at 44 °C.

2.2.2. Preparation of microparticles via emulsion solvent evaporation

For purposes of comparison, microparticles were also prepared from an emulsion solvent evaporation method. Please see elsewhere for full details of the method [28]. Briefly, prednisolone-loaded Eudragit L and Eudragit S microparticles with a drug to polymer ratio of 1 to 30 were manufactured using an oil-in-oil (o/o) emulsion system with ethanol and liquid paraffin.

2.2.3. Encapsulation efficiency and yield

The encapsulation efficiencies were determined by dissolving 100 mg of the microparticles in 100 ml methanol. The resulting solution was aliquoted and 10 ml dispensed into a volumetric flask, followed by the addition of 0.1 M HCl to precipitate the pH-sensitive polymer. After precipitation, the volume was made up to 100 ml. Samples were filtered through 0.22 μm Millex filters, and the drug content was analyzed by UV spectrophotometry at a wavelength of 247 nm. The experiment was carried out in triplicate for each sample.

Drug encapsulation efficiency is calculated from:

$$\text{Encapsulation efficiency } (\%) = \frac{\text{Calculated mass of drug in the microparticles}}{\text{Theoretical mass of drug in the microparticles}} \times 100 \quad (1)$$

The yield of microparticles for each batch was calculated as follows:

$$\text{Yield}(\%) = \frac{\text{Mass of harvested microparticles}}{\text{Mass of solid content in feed solution}} \times 100 \quad (2)$$

2.2.4. Microparticle size and aggregation tendency

Median particle size and size distribution were assessed using laser diffraction analysis (Malvern Mastersizer, Malvern Instruments). Each sample was suspended in 0.1 N HCl solution. Post-dissolution aggregation was measured, whereby a 10 ml sample was retrieved from each vessel after 15 min. All readings were taken in triplicate.

2.2.5. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to analyze the morphology of the microparticles. Samples were coated with gold using a K550 sputter coater (Emitech, Ashford, Kent, UK) and observed using a Philips/FEI XL 30 SEM (Phillips, Cambridge UK) at 10 kV.

Table 1
Formulation and preparation variables for the Eudragit S microparticles.

Formulation	Polymer con. (w/v %)	Feed rate (%)	Inlet temperature (°C)	Outlet temperature (°C)	Additive(s) (w/w)	Time of incubation at 70 °C (min)
F1	1	18	90	48	–	–
F2	2	18	90	48	–	–
F3	4	18	90	48	–	–
F4	2	18	90	45	–	60, 120 and 180
F5	2	18	90	45	Sorbitan sesquioleate 5%	60, 120 and 180
F6	2	18	90	45	Sorbitan sesquioleate 5%, GMS 5%	180

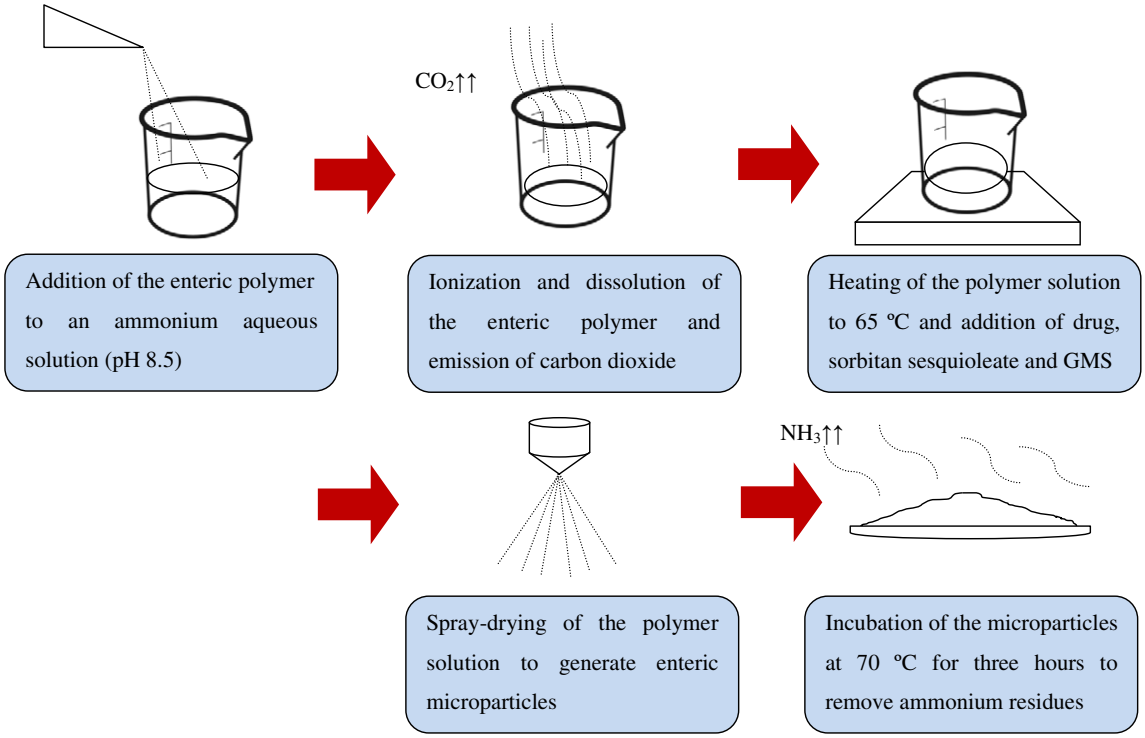

Fig. 1. Steps involved in the fabrication of enteric microparticles from spray drying an aqueous solution.

2.2.6. Fourier transform infrared (FTIR)

FTIR was used to determine residual ammonium content of the spray-dried microparticles. Absorbance of the samples was measured using a Nicolet™ FTIR spectrometer. After completing a background scan, the samples were scanned 32 times and an average spectrum was determined. The wavelength of interest was 1525–1550 cm^{-1} corresponding to the stretching of the N–H bond.

2.2.7. In vitro release and determination of the pH dissolution threshold of the enteric microparticles

The USP27 paddle method was employed to assess the dissolution behavior of the microparticles. Microparticles (200 mg) were accurately weighed and filled into two size 0 capsules. Each capsule was placed in a separate metal basket in a vessel containing 750 ml of 0.1 N hydrochloric acid. After 120 min, 250 ml of 0.2 M tri-sodium phosphate pre-equilibrated to 37 ± 0.5 °C was added to each vessel and the pH of the solution adjusted to pH 6.8 ± 0.05 when testing Eudragit L particles, and pH 7.4 ± 0.05 when testing Eudragit S microparticles. The speed of the paddle was set at 100 rpm and the temperature of the solution was 37 ± 0.5 °C. Each dissolution test was carried out in triplicate. Prednisolone release was determined at 247 nm using a UV–Vis spectrophotometer. A standard calibration curve of prednisolone was prepared in acidic and buffer media. The absorbance of blank microparticles following the same dissolution test conditions was measured and subtracted from that of drug-loaded microparticles to exclude any interference.

To investigate the pH threshold of drug release for the spray-dried Eudragit S and Eudragit L microparticles, dissolution tests were carried out using 750 ml of 0.1 N hydrochloric acid for two hours followed by the addition of 250 ml of 0.21 M, 0.2 M, 0.192 M, 0.17 M, 0.156 M, or 0.152 M tri-sodium phosphate pre-equilibrated to 37 ± 0.5 °C to attain pH values of 7.4, 6.8, 6.4, 6.0, 5.5, or 5.0, respectively. The pH of the medium was adjusted if necessarily with 5 N NaOH solution.

To provide a more realistic simulation of the fluids of the small intestine, Kreb's and modified Hanks (mHanks) bicarbonate buffers were utilized to test the dissolution properties of the enteric microparticles. The buffers were stabilized by purging with a gas stream of CO_2 5% (95% oxygen) [29]. Kreb's buffer (pH 7.4) was composed of 1.18 mM KH_2PO_4, 24 mM $NaHCO_3$, 118.07 mM NaCl, 4.69 mM KCl, 2.52 mM $CaCl_2$, and 1.18 mM $MgSO_4{\cdot}7H_2O$ (pH adjusted to 7.4 using 5 M HCl), and was used to evaluate the Eudragit S microparticles. A modification of Hank's buffer (mHanks) was used to test the Eudragit L microparticles at pH 6.8; the medium was composed of 136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4{\cdot}7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4{\cdot}2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM $NaHCO_3$, and sufficient CO_2 (g) to reach a pH of 6.8 [30].

3. Results and discussion

The SEM images reveal that spherical microparticles with acceptable morphology were produced using the aqueous ammonium solution of Eudragit S (Fig. 2a–f).

Upon introduction to the dissolution medium, the Eudragit S microparticles prepared from three different starting concentrations of polymer (1, 2 and 4% w/v) aggregated in acid and were unable to control drug release (Fig. 3). Interestingly, the extent of drug release in acid was inversely proportional to the starting concentration of polymer in the feed solution. FTIR spectra of these microparticles indicated the presence of the ammonium salt with a peak at 1550 cm^{-1} corresponding to N–H bond stretching (Fig. 4). The intensity of this peak increased at higher concentrations of polymer solution. It can be assumed that this is due to a lower heat mass transfer with higher polymer solution concentration. This resulted in more efficient removal of the ammonium salt at lower concentrations of the feed solution. The presence of this salt increased the solubility of the polymer in the acidic environment and in turn compromised the acid-resistant properties of the Eudragit S microparticles.

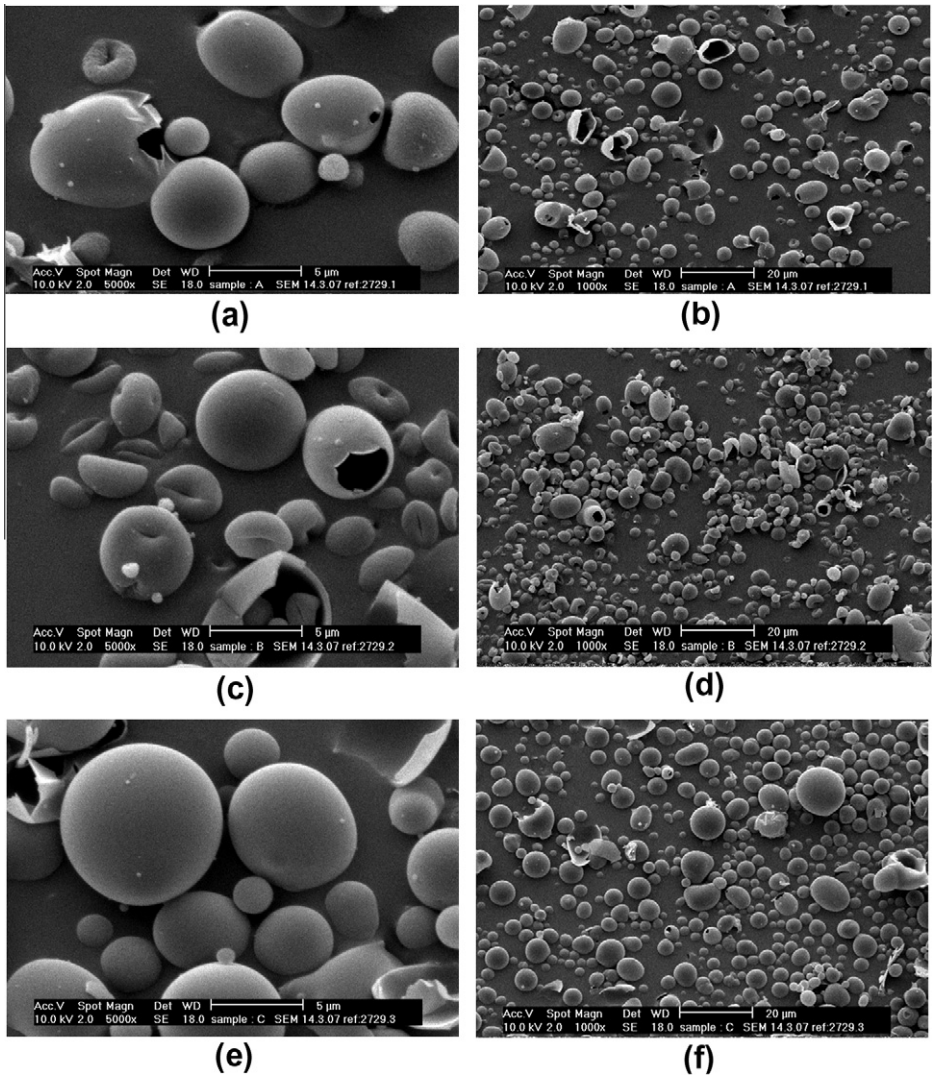

Fig. 2. SEM images of Eudragit S microparticles prepared from formulation F2 (a and b), formulation F3 (c and d) and formulation F5 (e and f).

It was expected that elevating the outlet temperature during spray-drying to above 60 °C would aid in the removal of the ammonia residues. However, increasing the outlet temperature appeared to have little impact on the ammonium content of the microparticles as confirmed through FTIR analysis and drug release data (data not shown). This may be due to the incomplete degradation of ammonium hydrogen carbonate residue or insufficient time of heat treatment during the spray-drying process. Therefore, the utilization of higher temperatures for a longer period of time was deemed necessary to remove all the ammonia residues and regenerate the acidic form of the Eudragit S polymer in the microparticles. The microparticles were subjected to a heat treatment of 70 °C for 60, 120 and 180 min (F4a, F4b and F4c). It was considered important to subject the microparticles to a heat treatment of 70 °C for 180 min to minimize the concentration of ammonium in the microparticles (Figs. 5 and 6). The addition of the surfactant, sorbitan sesquioleate, improved the quality of the microparticles (F5), and the inclusion of glyceryl monostearate increased the hydrophobicity of the microparticle product (F6) and prevented gel formation in acid.

Formulation 6 (F6) was chosen as the "gold standard" formulation since the microparticles were gastro resistant, and displayed good morphology and acceptable dispersion in dissolution media. Using this formulation as a basis, Eudragit L microparticles were also fabricated. However, it was necessary to incubate the Eudragit L microparticles at 130 °C to eradicate the ammonium residues (data not shown). Fig. 7 shows the SEMs of Eudragit S and Eudragit L microparticles (particle size of 33.8 ± 2.7 μm and 35.6 ± 3.5 μm with span 5.2 ± 2.5 and 4.3 ± 2.6, respectively). The encapsulation efficiency and yield were 87.8 ± 9.1% and 23.4% for Eudragit S microparticles, and 100.1 ± 1.3 and 30.8% for Eudragit L microparticles, respectively.

The relatively low yield is related to the low batch size used (8 g) compared to the minimum solid material normally required for spray-drying using a Niro SD Micro (200 g). Moreover, owing to the sticking of the polymer to the walls of the spray cylinder, cyclone, and tubing, small quantities of microparticles reached the collecting container.

After 2 h in acid, the release of drug was lower in the case of the Eudragit S microparticles (7.3%) compared to the Eudragit L microparticles (25.1%) (Fig. 8). The higher drug release from particles prepared from Eudragit L might be related to the lower pH threshold and higher number of methacrylic acid groups in the polymer compared to the Eudragit S polymer. It is feasible that a greater percentage of the carboxylic groups in Eudragit L were neutralized with ammonium during the preparation of the feed solution and some of these remained neutralized after the heat treatment.

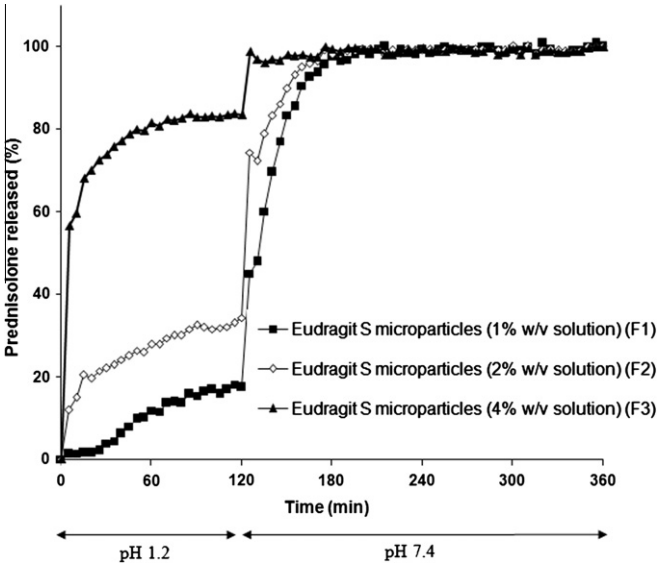

Fig. 3. Effect of polymer solution concentration on *in vitro* release profile of Eudragit S microparticles (F1, F2 and F3).

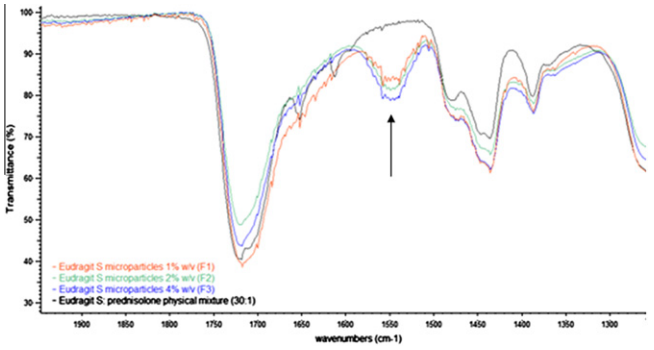

Fig. 4. FTIR spectra of Eudragit S: prednisolone (30:1) physical mixture, Eudragit S microparticles spray-dried from polymer solutions 1% (F1), 2% (F2) and 4% w/v (F3). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

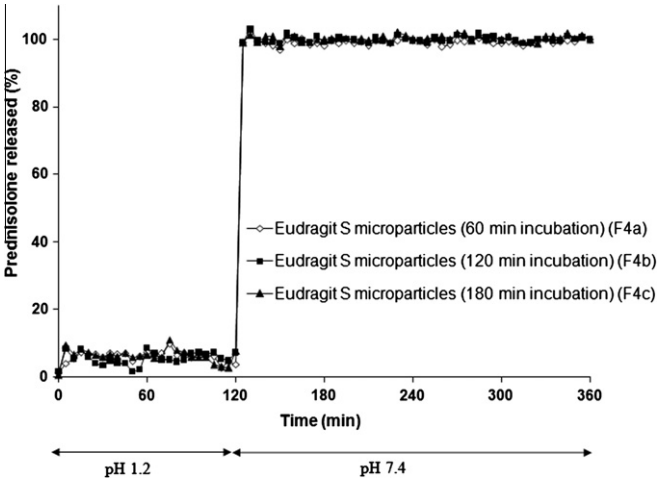

Fig. 5. Effect of time of incubation at 70 °C on drug release from Eudragit S microparticles (F4).

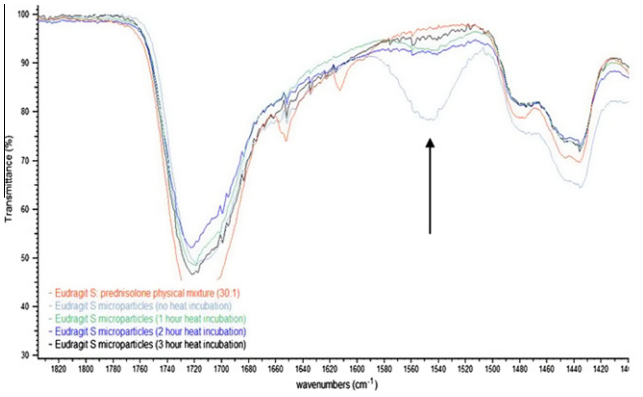

Fig. 6. FTIR spectra of Eudragit S: prednisolone (30:1) physical mixture (red line), Eudragit S microparticles (F4) spray-dried from polymer solutions before heat treatment (light blue line) and after heat treatment for 60 min, 120 min and 180 min. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Due to their acidic nature, enteric polymers have very low solubility in water and acid. One approach to enhance the solubility of an enteric polymer is through ionizing its acidic groups. Alkaline solutions can render an enteric polymer soluble and potentially amenable to spray-drying. Previous workers have utilized sodium hydroxide to solubilize the polymer in the feed solution to prepare microparticles via spray-drying [8,9]. On addition of the microparticles to acidic conditions, the retained sodium hydroxide will dissolve quickly and elevate the local pH near the microparticles, leading to dissolution and limiting gastric resistance. One approach to resolve this problem is to replace sodium hydroxide with ammonium solution such as ammonium hydroxide or ammonium hydrogen carbonate. Unlike with sodium hydroxide, ammonium salts can be eradicated by the use of elevated temperature (60–70 °C). This approach has been used previously in the enteric coating of tablets and pellets [25,31–34]. During the coating process, ammonium will be partly removed by the temperature in the drying chamber. It is also possible that during the gastric phase of the dissolution test, the strong hydrochloric acid may displace the weaker acidic groups of the enteric polymer (usually pKa = 3–7) in its ammonium salt, and hence convert the enteric polymer to its acidic form [35]. Unlike ammoniated enteric-coated systems, in the case of microparticles, drug will be entrapped within the matrix structure. The presence of the ammonium salt will invite water imbibition into the microparticle matrix, leading to polymer gelling, the formation of lumps and premature release of drug to the acid medium.

In our system, the enteric polymers will ionize in ammonium hydrogen solution rendering the polymer soluble (Eq. (3)). During the dissolution process, weak carbonic acid will degrade into water and carbon dioxide (Eq. (4)). In the drying process of the droplet, the heat will induce the donation of a proton from the ammonium group to the carboxylate group of the polymer, resulting in the restoration of the acidic form of the polymer and the evaporation of ammonia (Eq. (5)).

$$R{-}COOH + NH_4HCO_3 \rightleftarrows R{-}COO^{-}NH_4^{+} + H_2CO_3 \quad (3)$$

$$H_2CO_3 \rightleftarrows H_2O + CO_2 \quad (4)$$

$$R{-}COO^{-}NH_4^{+} \overset{\Delta}{\rightleftarrows} NH_3 + R{-}COOH \quad (5)$$

This novel production method of enteric microparticles, which involved polymer ionization, spray-drying and the regeneration of acidic groups, is expected to induce significant changes in the

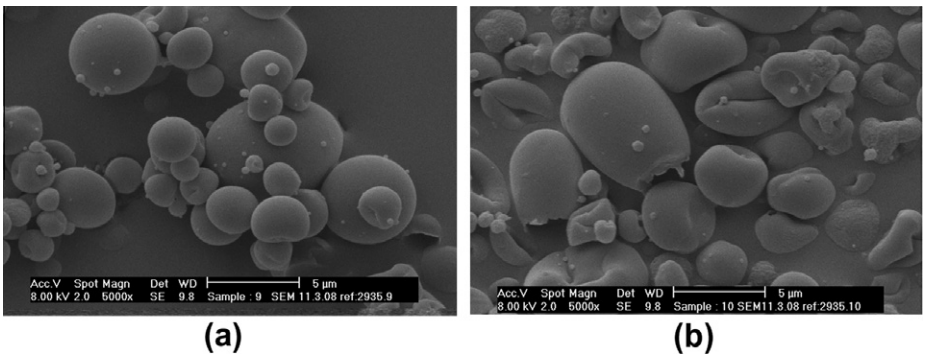

Fig. 7. SEM micrographs of (a) Eudragit S (F6) and (b) Eudragit L microparticles (equivalent to F6).

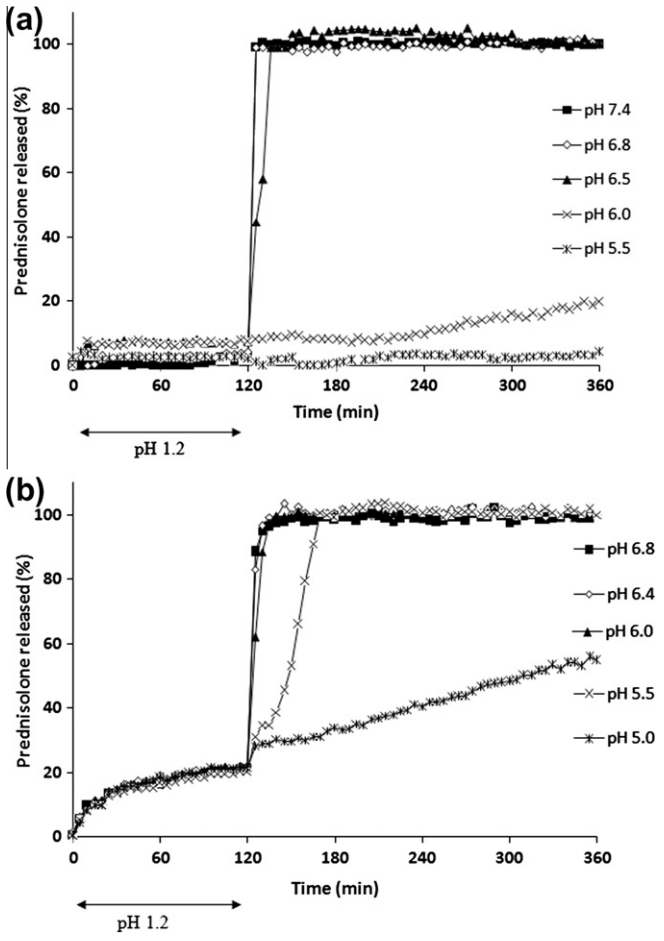

Fig. 8. In vitro prednisolone release from (a) Eudragit S microparticles (F6) (2 h in acid followed by changing the pH to 5.5, 6.0, 6.5, 6.8 or 7.4) and (b) Eudragit L microparticles (2 h in acid followed by changing the pH to 5.0, 5.5, 6.0, 6.4 or 6.8).

structure of the microparticle matrix compared to microparticles produced by emulsion solvent evaporation. Therefore, the pH thresholds of drug release as well as the *in vitro* dissolution in simulated intestinal buffers of Eudragit S and Eudragit L microparticles produced by both technologies were compared.

The USP II dissolution profiles of Eudragit L and Eudragit S microparticles were conducted in acid for two hours followed by four hours in phosphate buffers at different pH values in the range 5.0–7.4 (Fig. 8). Interestingly, although visual assessment of the dissolution vessel suggested that the majority of the microparticles did not dissolve, complete drug release was achieved at pH 6.5 and pH 5.5 for the Eudragit S and Eudragit L microparticles, respectively. These pH thresholds are lower than the pH dissolution of

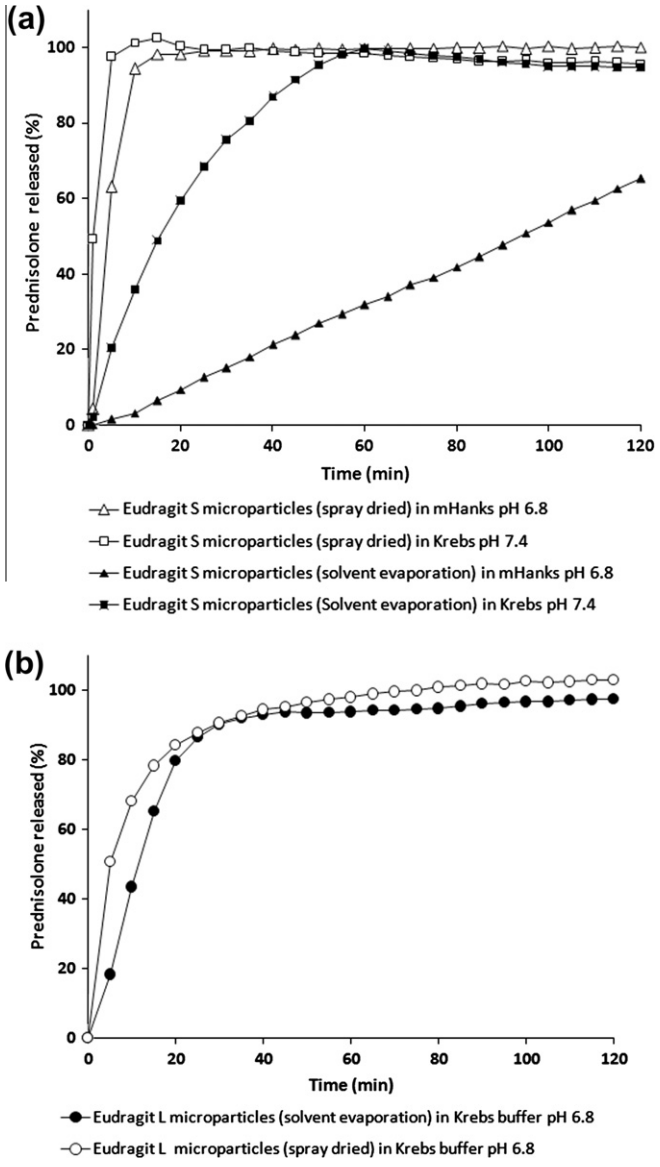

Fig. 9. In vitro release profile of prednisolone from (a) Eudragit S microparticles prepared by spray drying and solvent evaporation in modified Hanks (pH 6.8) and Kreb's (pH 7.4) bicarbonate buffer and (b) Eudragit L microparticles prepared by spray drying and solvent evaporation in modified Hanks (pH 6.8) bicarbonate buffer.

the native polymers (pH 7 and 6). At a pH value close to the dissolution threshold of the polymer, it is possible that a proportion of the methacrylic groups ionize leading to repulsion between the polymer chains. This might not allow complete polymer chain disengagement and dissolution, but may increase inter-chain space to a sufficient extent that allows prednisolone to diffuse through the polymer matrix to the dissolution medium.

Although phosphate buffers are commonly employed in dissolution testing, they only simulate the pH of intestinal fluid. Other parameters such as ionic strength and composition and buffer capacity are also influential. This is particularly important for the dissolution properties of ionized polymers and active pharmaceutical ingredients [36]. While phosphate buffer has a high buffer capacity (23 mM/L/pH unit), Kreb's bicarbonate buffer has a similar buffer capacity (5.45 mM/L/pH unit) to the fluids of the distal small intestine (6.4 mM/L/pH unit) [37]. In fact, Kreb's buffer showed significant advantages over phosphate buffers in predicting drug solubility [29] and the *in vivo* performance of enteric-coated formulations for ileo-colonic delivery [38–40]. More recently, a modified version of Hanks buffer (mHanks, pH 6.8, buffer capacity 3.1 mM/L/pH unit) provided a good simulation of the proximal small intestine [30]. Therefore, the *in vitro* release of Eudragit S and Eudragit L microparticles produced through emulsion solvent evaporation (particle size $dv_{(0.5)}$ = 47.9 and 37.6 μm respectively) [28] and spray-drying was evaluated in bicarbonate buffers.

Spray-dried Eudragit S microparticles showed a faster release than the corresponding microparticles prepared by emulsion solvent evaporation (Fig. 9a) at pH 6.8 and pH 7.4. However, both Eudragit microparticles did not completely dissolve at pH 6.8 despite prednisolone release from the microparticles. This can be attributed to the lower-density matrix, partially neutralized methacrylic groups of Eudragit S and the smaller particle size of spray-dried microparticles compared to the microparticles produced by emulsion solvent evaporation. Eudragit L spray-dried microparticles showed slightly faster drug release than the microparticles prepared by emulsion solvent evaporation (Fig. 9b). The highly pH-sensitive nature of these microparticles can be advantageous for site-specific delivery applications in the gastrointestinal tract.

4. Conclusion

A novel method to produce pH-sensitive microparticles from aqueous solutions through spray-drying has been developed. The microparticles showed spherical morphology compared to previous attempts based on aqueous or organic solutions. Both the Eudragit L and S microparticles displayed gastric-resistant properties. On changing the pH to intestinal values (pH 7.4 for Eudragit S and pH 6.8 for Eudragit L), rapid and complete drug release was reported. Interestingly, the Eudragit S and Eudragit L microparticles had unique properties; the preparation process lowered the pH threshold of the Eudragit S and Eudragit L microparticles to 6.5 and 5.5, respectively. In Kreb's and mHanks bicarbonate buffers, Eudragit S and L microparticles showed a highly pH-sensitive response to the pH of the media. This new spray-drying approach avoids the need for organic solvents and utilizes conventional industrial processes and therefore provides economic, safety, and environmental benefits.

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