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Effects of coating layer and release medium on release profile from coated capsules with Eudragit FS 30D: an *in vitro* and *in vivo* study

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ABSTRACT

The aim of the present research was to evaluate the impact of coating layers on release profile from enteric coated dosage forms. Capsules were coated with Eudragit FS 30D using dipping method. The drug profile was evaluated in both phosphate buffer and Hank's solutions. Utilization X-ray imaging, gastrointestinal transmission of enteric coated capsules was traced in rats. According to the results, no release of the drug was found at pH 1.2, and the extent of release drug in pH 6.8 medium was decreased by adding the coating layers. The results indicated single-layer coated capsules in phosphate buffer were significantly higher than that in Hank's solution. However, no significant difference was observed from capsules with three coating layers in two different dissolution media. X-ray imaging showed that enteric coated capsules were intact in the stomach and in the small intestine, while disintegrated in the colon.

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Introduction

In recent years, colon-targeted drug delivery is one of the most considered routes for its potential to lower drug dose and side effects, reduce digestive enzymatic activity as well as the potential to improve drug delivery to colon in condition such as colon cancer and inflammatory bowel disease (IBD) [1,2]. Oral administration is the most preferred delivery route for colon targeting because of its ease and safe administration, not requiring sterling and improved patient compliance [1,3]. In addition, by increasing drug retention time in colon, targeted drug delivery to colon can improve the systemic bioavailability of drugs which are poor absorbed [4]. Considering such advantage, different approaches are examined for oral specific drug delivery to colon, including pH, time, microflor, and pressure-sensitive polymers [2,5]. Implication of these approaches may delay the release of drug until reaching the colon. Eudragit® FS 30D, an anionic copolymer of methyl acrylate, methacrylic acid, and methyl methacrylate is employed for colonic-targeting drug delivery. Because the presence of methacrylic acid group in its structure solubility of Eudragit FS 30D in aqueous medium is pH dependent [6–8]. It is considered as a pH dependent polymer which retards drug release in small intestine [8]. Nevertheless, due to pH similarity between small intestine and the colon, employing of a single pH dependent system is not suitable for colon delivery [9]. To overcome this problem, the combination of pH and time sensitive polymers is proposed for decreasing the release in the small intestine and consequently releasing the drug in the colon [10]. However, in the study we introduced a single pH dependent system with increasing coating layers that would allow the capsule dosage form to pass the small intestine unchanged and to start releasing the drug at the colon. This approach leads to lower cost and reduces the processing time of the final dosage form. Moreover, the drug release was evaluated in both, phosphate buffer and Hank's buffer solutions. Phosphate buffer is frequently used as media for determining the release profile of drugs. However, the concentration of ionic is considerably different in phosphate buffers and the real intestinal fluid. Therefore, due to the probability of interaction between coating material and basic ions, determination of rate drug release through enteric coated capsules can be misleading [11]. On the other hand, for *in vitro* dissolution tests to be valid, they require to simulate *in vivo* conditions. Physiological salt solution Hank's buffer resembles the ionic composition of small intestinal environment [12]. The aim of the present study was to compare the release profile of the drug from capsules coated with Eudragit FS 30D as a pH dependent polymer in phosphate buffer and Hank's solution with appropriate coating thickness in order to deliver most of the drug to the colon. To our knowledge, this is the first study that evaluates a multilayer pH-dependent system for more effective drug release in the colon. Theophylline, a water soluble molecule was chosen as drug model, and the transportation of enteric coated capsules in rat gastrointestinal (GI) tract was traced by X-ray imagining method.

Material and methods

Eudragit® FS 30D and theophylline were kindly donated by RÖhm GmbH (Darmstadt, Germany) and Dr. ABIDI Pharmaceutical Co.,

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Tehran, Iran, respectively. Glyceryl monostearate (GMS) and triethyl citrate (TEC) were obtained from Sigma (Germany). Tween 80 and methyl orange were acquired from Merck (Germany). Size 9 capsules were purchased from Capsugel (Belgium). Barium sulfate ($BaSO_4$) was obtained by Darou Paksh Pharmaceutical Mfg. Co., Tehran, Iran. Gastrografin was purchased from BerliMed S.A. (Spain), and male Wistar rats were provided from the Pasteur Institute of Iran.

Preparation of enteric coated capsules

In this investigation, coated capsules were prepared by dip-coating method, mainly because this is a simple technique, requiring inexpensive equipment and provide results in shorter periods of time. The Eudragit® FS 30D dispersion was prepared according to RÖhm protocol. GMS (7.2 g) as a glidant, tween 80 (33% aqueous solution, 8.8 g) as an emulsifier, and TEC (9 g) were added to 30% of the total water (377.3 g) which was heated to 70–80 °C. Then, it was stirred for 10 min. The remaining 70% of water was poured to this emulsion. Then the suspension was slowly added into the Eudragit dispersion under constant mixing.

Gelatin capsules (size 4) were manually filled with methyl orange as an indicator dye and theophylline as drug model. Then capsules were coated by dipping once, twice, and three times in Eudragit FS 30D dispersion followed by drying at room temperature. For *in vivo* imaging studies, size 9 capsules were filled manually with $BaSO_4$ and then immersed in solution coating. The schematic of preparation of enteric coated solution and dipping method are shown in Figure 1.

Drug release measurement

Release of theophylline from coated capsules was measured using basket method in 500 ml dissolution medium maintained at 37.0 ± 0.5 °C and at a 100 rpm rotation speed. The tests were conducted under sink conditions. A pH change technique was used involving dissolution in 0.1 M HCl (pH 1.2) for 2 h to simulate gastric fluids, followed by 3 h in two buffer media; phosphate buffer (pH 6.8) to simulate small intestine as well as in a Hank's buffer

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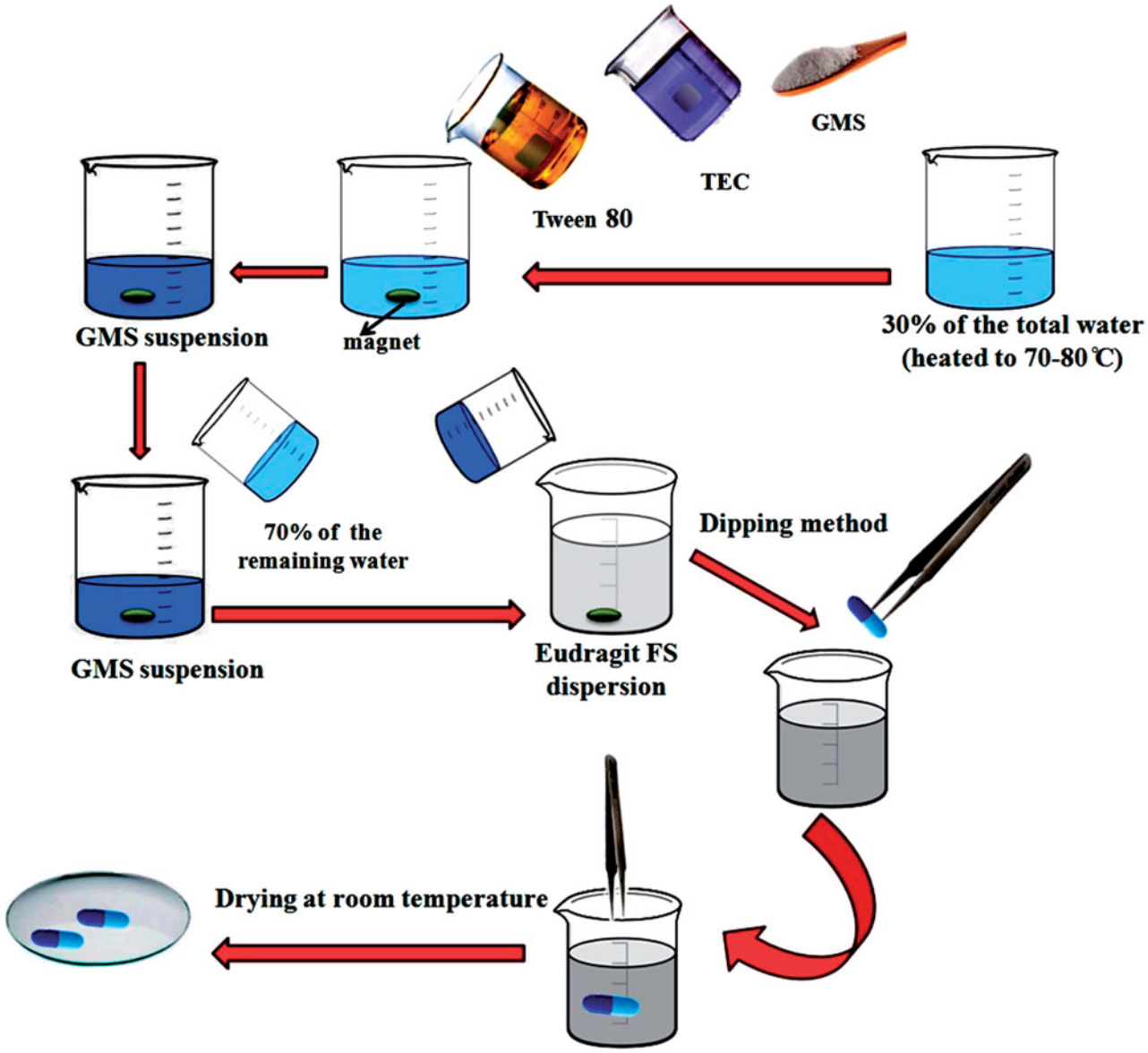

Figure 1. The schematic of preparation of enteric coated solution and dipping method.

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which its ionic composition is similar to intestinal fluid. Then pH 7.4 phosphate buffer was used to test for drug release for 3 h as simulated colonic milieu [5,13,14]. In order to determine the released drug in each dissolution medium, 5 ml of the mediums were withdrawn and equal volumes of fresh medium were replaced. The concentration of released drug was then determined using a UV spectrophotometer (Biochrom WPA biowave II, England) at 272 nm. The electrolyte composition of Hank's buffer, phosphate buffer and in the human small intestinal fluid are shown in Table 1.

Drug release kinetic models and their mean dissolution times (MDT) were considered as the basis for comparison of the dissolution rates. MDT was calculated by the following equation:

$$MDT = \int_0^{W\infty} t.\frac{dW(t)}{\int_0^{W\infty} dW(t)} \quad (1)$$

where $W(t)$ is the cumulative amount of drug dissolved at time t.

Moreover, dissolution efficiency (DE) was calculated according to Equation (2)

$$DE = [AUC_{0-T}/\%D_{max}.T].100 \quad (2)$$

where $\%D_{max}$ is the maximum dissolved drug at the final time T and AUC_{0-T} is the area under the curve from zero to T.

Morphological properties

Scanning electron microscopy (SEM, LEO, 1455VP, Germany) was used to evaluate the surfaces of the coated and uncoated capsules. Further in order to confirm the coating, capsules were mechanically cleaved cross-sectional and photographed by SEM. The thickness of coated capsules was also determined by SEM.

Table 1. Comparison of the electrolyte concentrations and characteristics of tested buffer media and small intestinal fluid [11,13].

	Phosphate buffer	Hank's buffer	Small intestine
Na^+ (mM)	39.5	141.7	140
K^+ (mM)	50	5.8	4.9
Cl^- (mM)	–	142.9	125
Ca^{2+} (mM)	–	1.3	4.2
Mg^{2+} (mM)	–	0.8	2.8
HCO_3^- (mM)	–	4.2	30
HPO_4^{2-} (mM)	39.5	0.3	–
SO_4^{2-} (mM)	–	0.8	–
$H_2PO_4^-$ (mM)	10.5	0.4	–
Osmolality (mOsm/kg)	228	295	292
Ionic strength	0.129	0.155	0.139
Buffer capacity (mmol/L/pH unit)	23.0	1.0	5

In vivo X-ray imaging studies

The animal studies were conducted according to the guideline of the Animal Ethics Committee Jundishapur University of Medical Sciences, Ahvaz, Iran (ref no. IR.AJUMS.REC.1395.643). Male, Wistar rats, weighing 250–300 g were fasted overnight with free access to water. After an overnight fasting, gastrografin (10%) was administrated to rats by oral gavage. Gastrografin is a contrast material for the radiological examination of the gastrointestinal tract. Then, rats received orally $BaSO_4$ capsules coated with Eudragit FS 30 D. X-ray images of the gastrointestinal tract (GIT) of rats were taken at different time intervals to trace the movement and behavior of coated capsules (Toshiba, ROTANODE™, Japan). Optimal imaging conditions were obtained with X-ray beams of 50 ms and 55 kVp.

Statistical analysis

The presented data are the average of at least 5 individual experiments and are presented as means ± SD. Two groups were compared by the nonparametric test. A difference of $p < 0.05$ was considered statistically significant.

Results and discussion

In the study, for evaluation the effects of coating layers on the rate of drug release, capsules were immersed once, twice, and three times in Eudragit FS 30D dispersion. As shown in Figure 2, capsules remained intact at pH 1.2 (mimicking the acidic milieu in the stomach). These results confirmed the resistance feature of the Eudragit FS polymer in the acidic environment. The dissolution rate of the one immersion coated capsules in pH 6.8 was faster than capsules which dipped twice and three times. In other words, increases in coating layer thickness delayed drug release from enteric coated capsule in pH 6.8 (simulating the pH environment in the small intestine). The probable reason may be the more time needed for eroding thicker coating layers [15]. These findings seem to be consistent with other researches which found that sufficient coating influenced drug release. Among them, Akhgari et al. showed the effectiveness of the concentration of coating solution on retardation of indomethacin release in digestive tract. According to their results, in comparison to 10 and 15% coating solutions, a coating formulation consisted of 20% Eudragit S100 and L100 (as pH-dependent polymer) significantly delayed the

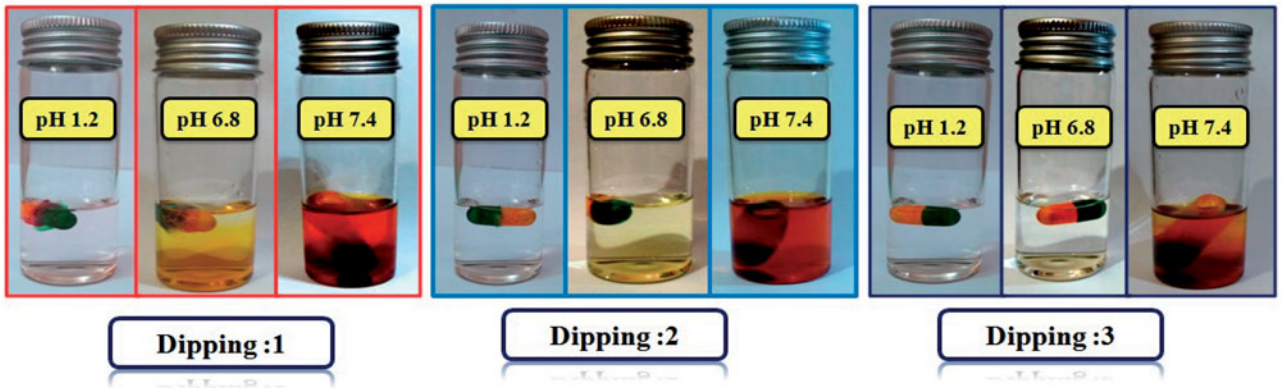

Figure 2. *In vitro* dissolution of coated capsules with one, two, and three layers of Eudragit FS in pH 1.2 (to mimic the gastric acidic medium), pH 6.0 (to simulate small intestine medium) and pH 7.4 (to simulate the colon environment).

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drug release from pellets [16]. Also, Liu et al. reported that by increasing the thickness of coating led to decrease the drug release [17]. Further in order to confirm which coating thickness is inversely relative to the drug release, enteric coated capsules containing theophylline were prepared by one and three times dipping in Eudragit FS 30 D dispersion (according to the results of Figure 2). As can be seen in the Figure 3, there was significant difference between the drug released from coated capsule which dipped one (20.29%) and three times (9.13%) in coating solution ($p < 0.05$) within 5 h in pH 6.8 phosphate buffer. It is reported that polymers used for colon targeting should be resist in the lower pH values of the stomach and the small intestine and moreover be able to disintegrate at pH of the colon [16]. Moreover, Eudragit FS 30 D as a pH-dependent polymer is better than to Eudragit L and Eudragit S for colonic delivery due to retarding drug release in the small intestine [8]. However, because of similarity and variation between small intestine and the colon, the single pH-dependent system would not be appropriate for colon specific delivery [9]. Moreover, premature drug release in the small intestine can lead to systemic absorption and resulting side effects [10]. It is suggested that combination of pH and time sensitive polymers as a coating material for colon targeted drug delivery can reduce the release of the drug in the small intestine and subsequently release the drug in the colon in a sustained manner [10]. The present findings agree with results of Naeem et al. which reported that pH and time dependent nanoparticles could efficiently maintain the loaded drug until reaching the colon [10]. Sharma et al. employed hydroxypropyl cellulose (HPC) and Eudragit S100 as time and pH dependent polymer, respectively for coating using dip immersion method. They observed that 94.05% of drug was released in pH 7.4 media. The coating combination of both polymers was successful in preventing the drug release in the upper part of GI tract [15]. In addition, Patel et al. developed a formulation using a combination of time (HPMC) and pH (Eudragit L100) dependent system for delivering mesalamine to the colon. They reported that this system passed intact through the small intestine to the colon and concluded that the system can be considered as drug delivery system for colon [18]. By comparing our results with other researchers, we can conclude that similar to the combination of pH and time dependent polymers, our system (pH dependent system with three coating layers) can be employed with high efficiency in the drug delivery to the colon. Furthermore, using single system to deliver drugs to the colon is economically affordable.

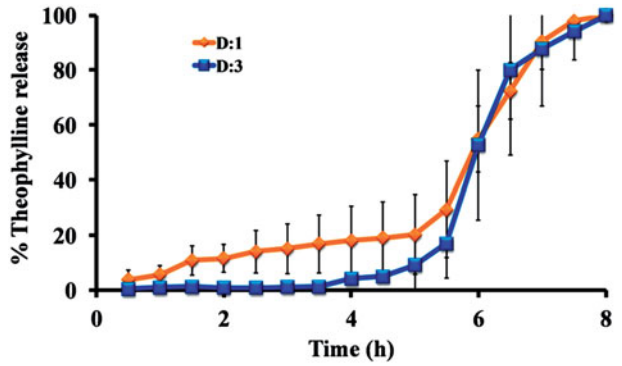

Figure 3. Drug release profile under continuous dissolution based on GI transit time (0–2 h at pH 1.2, 2–5 h at pH 6.8, 5–8 h at pH 7.4). (D: dipping).

Table 2. MDT and DE values for monolayer and triplicate coated capsules.

	Dipping: 1	Dipping: 3
MDT	0.27 ± 0.10	0.52 ± 0.08
DE	12.17 ± 6.50	2.10 ± 0.41

The results of MDT and DE values are shown in Table 2. Regarding the calculations, the MDT and DE values for monolayer coated capsules were less and more than triplicate coated ones, respectively. It was also observed that mono-dipped and triple-dipped capsules released their drug according to Peppas and Peppas-Wagner kinetic models, respectively.

The influence of coating layers on drug release rate was also evaluated in Hank's buffer which provides a better simulation of small intestinal fluids than phosphate buffer [11] as shown in Table 1. According to the Figure 4(A), drug release from capsules with one coating layer in phosphate buffer was significantly faster than in Hank's buffer. It is reported that the composition of the dissolution medium, particularly the buffer salts influences the dissolution rate of enteric polymers. A possible explanation for the faster dissolution observed in phosphate buffer compared to Hank's buffer is based on the Brönsted theory. According to the theory, the acid monomer units of Eudragit FS dissolve through the dissociation of the acids by transfer of proton to the base H_2O, resulting in the formation of the conjugate base of the polymer and hydronium ions [12]. By increasing the concentration of basic salts such as phosphate ions (HPO_4^{-2}), the rate of proton transfer is accelerated and therefore the dissolution rate increases [11,12]. In accordance with the literature, the release profiles in

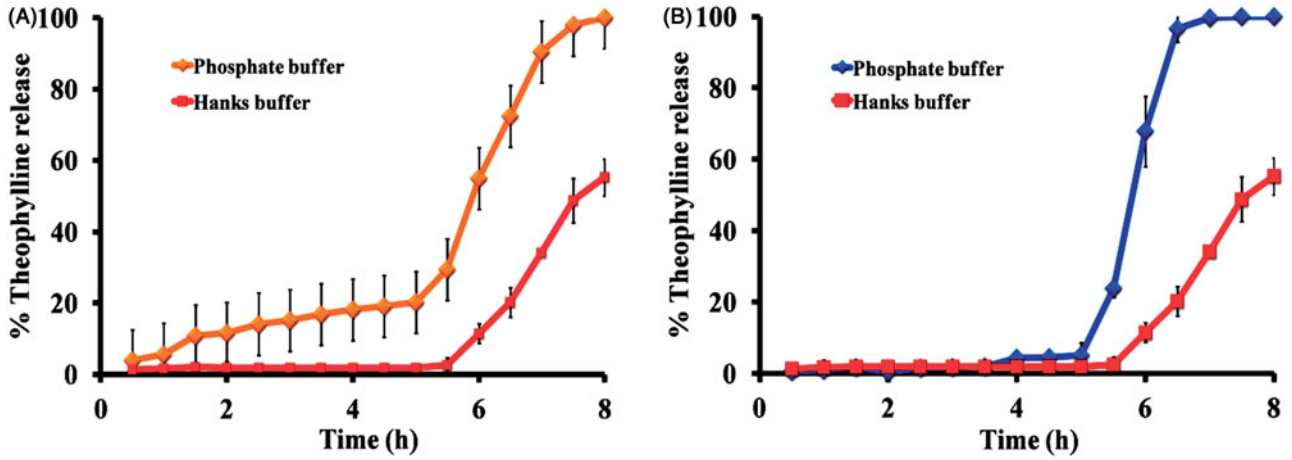

Figure 4. Drug release profile in Phosphate buffer pH 6.8 and Hank's buffer following 2 h exposure to acid. (A) dipping: 1 and (B) dipping: 2.

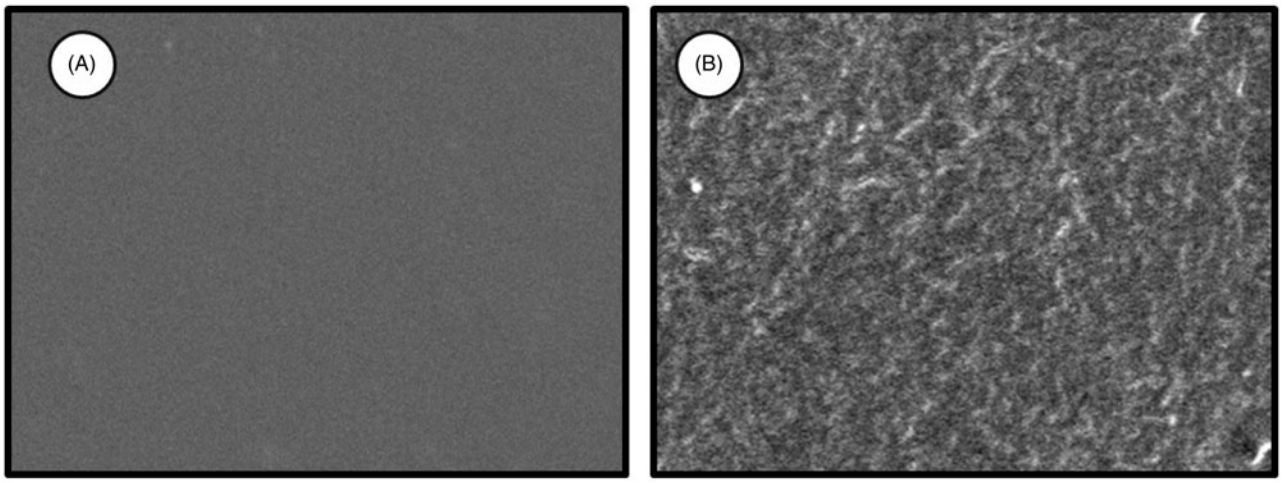

Figure 5. SEM image of the surface of (A) gelatin capsules and (B) coated capsule with Eudragit FS.

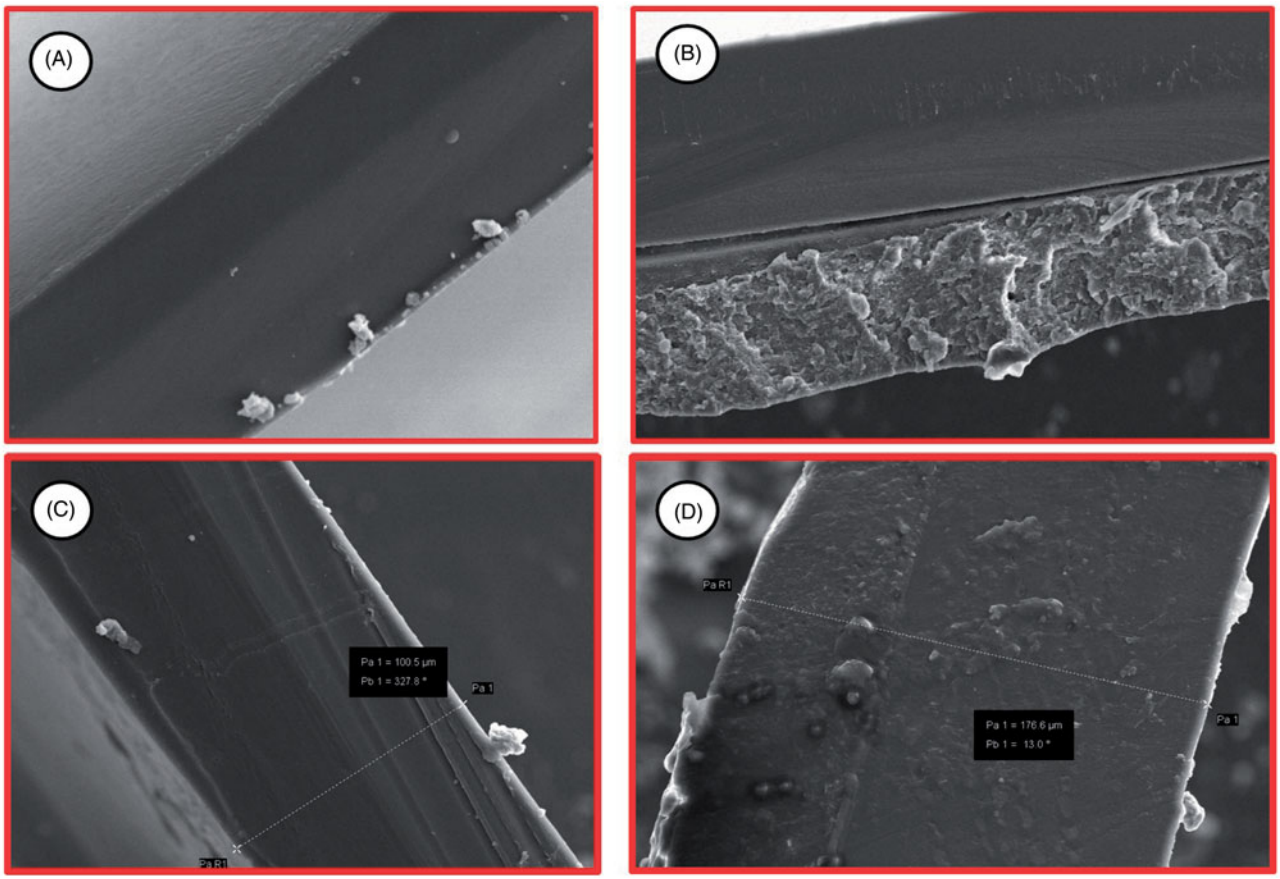

Figure 6. SEM image of the cross-section of a cleaved surface through (A) a non-coated capsule, (B) coated capsule with Eudragit FS and (C) the thickness of cross-section of uncoated capsule, and (D) coated capsule with Eudragit FS.

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different buffers may also be explained by buffer capacity. A low buffering capacity will decrease dissolution rate by retarding the formation of the anionic species. Phosphate buffer has higher buffer capacity in comparison with Hank's buffer. Hence, faster dissolution rate will be occurred in the phosphate buffer. The second important finding was that no significant difference observed in the rate of drug release in the phosphate and Hank's buffer from capsules with three coating layers ($p > 0.05$) (Figure 4(B)). It may be due to that capsules with higher thickness take longer time to release the drug, subsequently retarding the release of drug in small intestine. These finding are contrary to the results of Chan et al. that showed the drug release rate in the phosphate buffer was significantly faster than that in Hank's solution particularly by increasing the coating thickness [11]. The results indicated that in addition to the intestinal pH, ionic composition of the dissolution media and buffer capacity, drug release is dependent on the thickness of polymeric layer.

Due to lower release small intestine medium, the coated capsule with three times dipping in Eudragit FS 30D dispersion was selected for the next *in vivo* studies.

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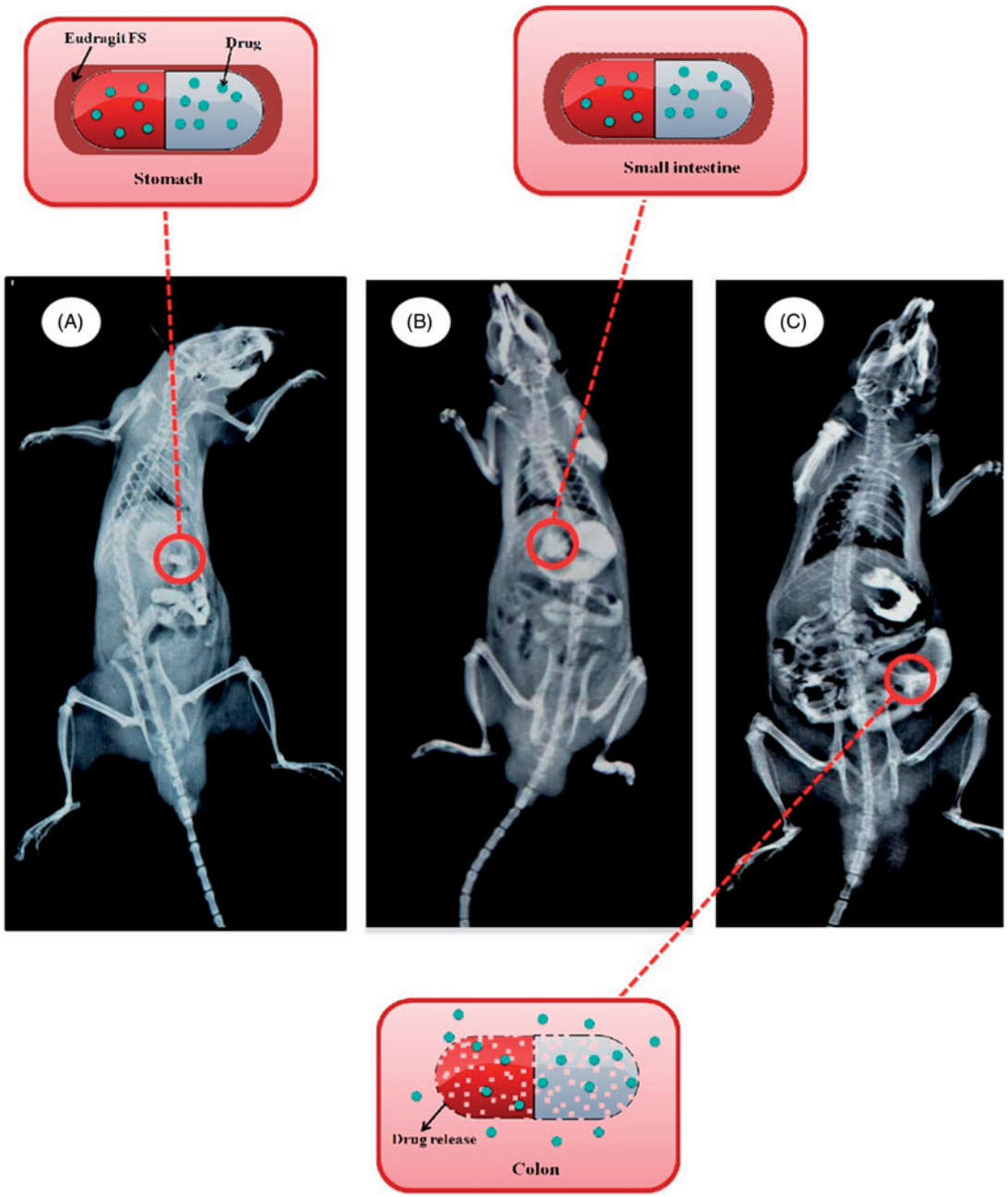

Figure 7. X-ray images of the movement of an enteric coated capsule (A) from the stomach (B) to the small intestine, and (C) to the colon.

Morphological properties

The morphology of surface of uncoated and coated gelatin capsules is shown in Figure 5(A,B). The surface of non-coated capsules was smooth while it was rough for coated ones. Figure 6(A,B) shows a SEM of the cross-section of a cleaved surface of gelatin capsule and capsule coated with Eudragit FS 30D. A higher amount of irregularities was observed around the cross-section of cleaved surface of enteric coated capsules which confirmed the coating. The thickness of uncoated and coated capsule surfaces is also shown in Figure 6(C,D). The surface thickness of gelatin capsule and enteric coated capsules were about 100.5 and 176.6 μm, respectively. These finding further confirmed the successful coatings of capsules with Eudragit FS. Based on the results of SEM and also results of release study, dipping technique can be employed as a rapid and simple method with high efficacy for coating capsules at laboratory scale.

In vivo *X-ray imaging studies*

X-ray technique is cheap, simple and by utilizing contrast media, simultaneous visualization of both capsule and the GIT is accessible [19]. The method was carried out in rats in order to follow the movement of the capsule in GIT. The results of X-ray imaging and mechanism of delivery system are presented in the Figure 7. According to the Figure 7(A), capsules remained intact in the stomach which confirms the gastro-resistant feature of Eudragit FS 30D. Afterward capsules reached the small intestine and remained in there for about 3 h. Finally, the capsule was completely disintegrated in the colon at 8 h after ingestion (Figure 7(C)). It is essential for colon drug delivery systems to protect the drug from being released in stomach and small intestine [20]. The present results obviously indicate that the coating capsules with three layers of Eudragit FS could be targeted specifically to the colon and prevent the drug release in stomach and small intestine.

These findings also imply the efficacy of dipping methods for coating of capsules.

Conclusion

In this study, by utilizing Eudragit FS as coating agent, the effects of coating layers on the drug release were evaluated using coated capsules with Eudragit FS. According to the results enteric coated capsules with three layers were more effective to protect the drug from being released in the small intestine and specifically delivering the drug to the colon. Capsules with one layer of Eudragit delayed the drug release in the Hank's solution. However, no significant difference was observed between the drug release from capsules with three layers of Eudragit in phosphate buffer and Hank's solution. *In vivo* results confirmed the delayed drug release in small intestine by employing capsules with three layer coatings. These findings also indicated the efficacy of dipping method for coating of capsules.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

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References

[1] Pinto JF. Site-specific drug delivery systems within the gastro-intestinal tract: from the mouth to the colon. Int J Pharm. 2010;395:44–52.
[2] Orlu M, Cevher E, Araman A. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. Int J Pharm. 2006;318:103–117.
[3] Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems: design trends and approaches. AAPS PharmSciTech. 2015;16:731–741.
[4] Wang QS, Wang GF, Zhou J, et al. Colon targeted oral drug delivery system based on alginate-chitosan microspheres loaded with icariin in the treatment of ulcerative colitis. International Journal of Pharmaceutics.2016; 515:176–185.
[5] Xing L, Dawei C, Liping X, et al. Oral colon-specific drug delivery for bee venom peptide: development of a coated calcium alginate gel beads-entrapped liposome. J Control Release. 2003;93:293–300.
[6] Zhang F. Melt-Extruded Eudragit® FS-based granules for colonic drug delivery. AAPS PharmSciTech. 2016;17: 56–67.
[7] Huyghebaert N, Vermeire A, Remon JP. Alternative method for enteric coating of HPMC capsules resulting in ready-to-use enteric-coated capsules. Eur J Pharm Sci. 2004;21: 617–623.
[8] Gao C, Huang J, Jiao Y, et al. In vitro release and in vivo absorption in beagle dogs of meloxicam from Eudragit FS 30 D-coated pellets. Int J Pharm. 2006;322:104–112.
[9] He W, Du Q, Cao DY, et al. Study on colon-specific pectin/ethylcellulose film-coated 5-fluorouracil pellets in rats. Int J Pharm. 2008;348:35–45.
[10] Naeem M, Choi M, Cao J, et al. Colon-targeted delivery of budesonide using dual pH- and time-dependent polymeric nanoparticles for colitis therapy. Drug Design Dev Ther. 2015;9:3789–3799.
[11] Chan WA, Boswell CD, Zhang Z. Comparison of the release profiles of a water soluble drug carried by Eudragit-coated capsules in different in-vitro dissolution liquids. Powder Technol. 2001;119:26–32.
[12] Liu F, Merchant HA, Kulkarni RP, et al. Evolution of a physiological pH 6.8 bicarbonate buffer system: application to the dissolution testing of enteric coated products. Eur J Pharm Biopharm. 2011;78:151–157.
[13] Ibekwe VC, Fadda HM, Parsons GE, et al. A comparative in vitro assessment of the drug release performance of pH-responsive polymers for ileo-colonic delivery. Int J Pharm. 2006;308:52–60.
[14] McConnell EL, Short MD, Basit AW. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. J Control Release. 2008;130:154–160.
[15] Sharma P, Chawla A, Pawar P. Design, development, and optimization of polymeric based-colonic drug delivery system of Naproxen. Sci World J. 2013;2013:12.
[16] Akhgari A, Afrasiabi Garekani H, Sadeghi F, et al. Statistical optimization of indomethacin pellets coated with pH-dependent methacrylic polymers for possible colonic drug delivery. Int J Pharm. 2005;305:22–30.
[17] Liu H, Yang XG, Nie SF, et al. Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: screening of formulation variables and in vitro investigation. Int J Pharm. 2007;332:115–124.
[18] Patel MM, Shah TJ, Amin AF, et al. Design, development and optimization of a novel time and pH-dependent colon targeted drug delivery system. Pharm Dev Technol. 2009;14:62–69.
[19] Aguirre TA, Aversa V, Rosa M, et al. Coated minispheres of salmon calcitonin target rat intestinal regions to achieve systemic bioavailability: comparison between intestinal instillation and oral gavage. J Control Release. 2016;238: 242–252.
[20] Luo JY, Zhong Y, Cao JC, et al. Efficacy of oral colon-specific delivery capsule of low-molecular-weight heparin on ulcerative colitis. Biomed Pharmacother. 2011;65:111–117.

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