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SEM/EDX and confocal microscopy analysis of novel and conventional enteric-coated systems

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ABSTRACT

A novel double coating enteric system (comprising an inner layer of neutralised EUDRAGIT® L 30 D-55 and organic acid, and an outer layer of standard EUDRAGIT® L 30 D-55) was developed to provide fast dissolution in proximal small intestinal conditions. The mechanisms involved in the dissolution of the double coating were investigated and compared with a conventional single layer enteric coating and an hypromellose (HPMC) sub-coated enteric system. Rates of drug release from coated prednisolone pellets were established using USP II dissolution methods (0.1 M HCl for 2 h and subsequently pH 5.5 phosphate buffer) and the coating dissolution process was illustrated using confocal laser scanning microscopy (CLSM). The distribution of sodium, as a representative ion, in the double-coating system during dissolution was determined using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX). The double-coating system showed faster dissolution compared to the single coating and the HPMC sub-coated system in pH 5.5 buffer. The dissolution process of the double-coating was unusual; the inner coat dissolved before the outer coat and this accelerated the dissolution of the outer coat. During dissolution, sodium ions diffused from the inner coat to the outer coat. This migration of ions and the increased ionic strength and buffer capacity of the inner coat contribute to the rapid dissolution of the double-coating system.

1. Introduction

Enteric-coated products for drug delivery to the small intestine normally disintegrate and dissolve rapidly *in vitro*. However, *in vivo*, such products take up to 2 h to disintegrate in the human small intestine (Bogentoft et al., 1984; Wilding et al., 1993; Ebel et al., 1993; Catteau et al., 1994; Lehmann et al., 1997; Cole et al., 2002; McConnell et al., 2008). It is therefore desirable to design enteric coatings that provide rapid release in the proximal small intestine, especially for drugs having a narrow absorption window or requiring rapid onset of action. A novel double-coated enteric system was developed for this purpose, using EUDRAGIT® L 30 D-55 as a model enteric polymer (Liu et al., 2009). The system comprises an inner layer of partially neutralised EUDRAGIT® L 30 D-55 and organic acid (such as citric acid or adipic acid), and an outer coat of standard EUDRAGIT® L 30 D-55 (Fig. 1). The previous study has proved that this double-coating system when applied to tablets was gastro-resistant and substantially accelerated the coating dissolution and drug release compared to a conventional enteric coating in simulated upper small intestinal conditions.

A number of mechanisms were proposed to explain the rapid dissolution of the double coating (Liu et al., 2009) and the present study aims to elucidate these by the application of sophisticated analytical techniques, for example confocal laser scanning microscopy (CLSM). CLSM has been extensively used in cell biology and recently applied to characterise pharmaceutical systems, such as film coating properties and drug release mechanisms within controlled-release dosage forms (Cutts et al., 1996; Melia et al., 1997; Guo et al., 1999, 2002; Lamprecht et al., 2003; Wolf et al., 2005; Bajwa et al., 2006). This technique was used to visualise the dissolution process of the double coating. For comparison purposes, CLSM was also utilised to investigate the dissolution of an hypromellose (HPMC) sub-coated enteric system and a conventional single layer enteric coating.

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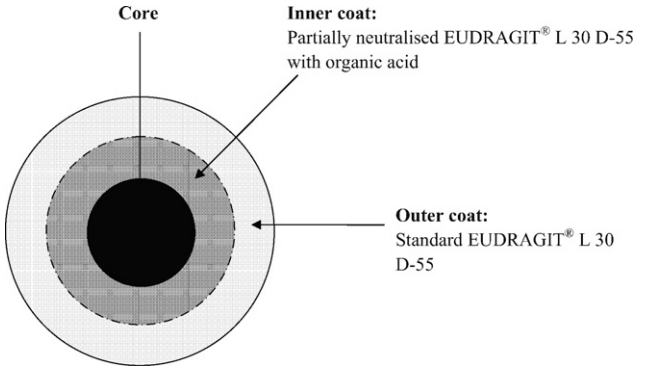


Fig. 1. Schematic of the double-coating concept.

The acidic EUDRAGIT® L 30 D-55 polymer and organic acid in the inner layer of the double coating were both partially neutralised by alkaline solution, and so formed salts. It was postulated that ions in the inner layer could migrate into the outer coat and assist its dissolution. This potential migration of ions was investigated using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX). EDX is a chemical microanalysis technique, performed in conjunction with SEM to allow the analysis of the chemical composition of a sample. It detects the specific energy of the emitted X-ray from each element of the sample caused by the bombardment of the electron beam from the SEM. The distribution of a certain element on the surface of the sample can be determined by conducting EDX mapping, which records the X-ray intensity of the element across the sample surface. Recently, a few studies have applied SEM/EDX to characterise pharmaceutical dosage forms (Tong and Gao, 2005; Ensslin et al., 2008; Reverchon et al., 2008).

The aim of the present study was to use the aforementioned analytical techniques to understand the underlying mechanisms involved in the dissolution of the novel double coating in comparison to conventional enteric coated systems.

2. Materials and methods

2.1. Materials

EUDRAGIT® L 30 D-55 was donated by Evonik Röhm GmbH, Darmstadt, Germany. EUDRAGIT® L 30 D-55 is the aqueous dispersion of the methacrylic acid-ethyl acrylate copolymer (monomer pK_a 4.6) with 30% solid content. The dissolution pH threshold of the enteric polymer is 5.5. The polymer (1 g) has an acid value equivalent to 300–330 mg KOH (Evonik Technical Bulletin, 2008). The pH of the dispersion is 2.8–3.0; the mean particle size in the dispersion is 0.25 μm (Lehmann, 1989). Adipic acid was purchased from Sigma–Aldrich Co. Ltd., Dorset, UK. Hypromellose 2910 (METHOCEL™ E5) was donated by Colorcon., Dartford, UK. Rhodamine B and fluorescein were obtained from Sigma–Aldrich Co. Ltd., Dorset, UK. Triethyl citrate was purchased from Lancaster Synthesis, Lancashire, UK. Talc (fine powder) was obtained from VWR International Ltd, Poole, UK. Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose was received from Ellis & Everard, Essex, UK. Microcrystalline cellulose (Avicel® PH101) was obtained from FMC Corporation, Philadelphia, USA. Urea was obtained from Sigma–Aldrich Co. Ltd., Dorset, UK. Placebo glass beads (spherical, 5 mm diameter) were supplied by Peco Laborbedarf GmbH, Darmstadt, Germany.

2.2. Preparation of prednisolone pellets

Each pellet contained 35% prednisolone, 40% lactose and 25% microcrystalline cellulose. Pellets were prepared by extrusion and spheronization using an extruder (model MX 50, J.J. Lloyd, Southampton, UK) and a spheronizer (GB Caleva Ltd., Sturminster Newton, UK). The pellets formed from the spheronization process were dried in an oven at 60 °C for 24 h and then sieved to obtain a size range of 0.71–1.0 mm.

2.3. Coating of prednisolone pellets

2.3.1. EUDRAGIT® L 30 D-55 single coating

Triethyl citrate (10% w/w, based on polymer weight) was dissolved into EUDRAGIT® L 30 D-55 dispersion. Talc (50%, w/w based on polymer weight) was homogenized in water and added into the above dispersion. The total solid content for the final dispersion was 20% w/w.

The recommended coating level for EUDRAGIT® L 30 D-55 to achieve enteric properties is in the range of 4–6 mg polymer (pure polymer) per cm^2 surface area of the core (Evonik Technical Bulletin, 2008). In the present study, 5 mg/cm^2 polymer was applied for the single coating. The pellets were coated using Strea-1 bottom spray fluidised bed coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions were: inlet air temperature 40 °C, outlet air temperature 30 °C, fan capacity 15 (equivalent to air flow 150 m^3/h), atomizing pressure 0.6 bar and spray rate 2.0 ml/min. After coating, the pellets were further fluidised for 15 min in the coater and cured in an oven at 40 °C for 2 h.

2.3.2. EUDRAGIT® L 30 D-55 double-coating

A number of double coating formulations were investigated in the previous paper with variable drug release profiles (Liu et al., 2009); a representative formulation having 15% adipic acid in the inner coat and neutralised to pH 5.6 was used in this study.

2.3.2.1. Inner coat. Adipic acid (15% w/w, based on polymer weight) and triethyl citrate (5% w/w, based on polymer weight) were dissolved in water, and added into EUDRAGIT® L 30 D-55 dispersion. The dispersion was then neutralised to pH 5.6 using 1 M NaOH. Since the dissolution pH threshold of the polymer is 5.5, the polymer particles in the EUDRAGIT® L 30 D-55 dispersion completely dissolved and the dispersion turned into a clear solution at pH 5.6. Talc (50% w/w, based on polymer weight) was homogenized in water and added to the solution to prepare a dispersion of 10% w/w total solid content.

As for the single coating the amount of polymer applied as the inner coat was 5 mg/cm^2. The coating conditions for the inner coating formulation were the same as the single coating except a lower spray rate (1.5 ml/min) was applied. After coating, the pellets were further fluidised for 15 min in the coater and subjected to the outer coating process.

2.3.2.2. Outer coat. The outer coat of the double coating was identical to the single coating. The amount of polymer applied was also 5 mg/cm^2. After applying the outer coat, the pellets were further fluidised for 15 min in the coater and cured in an oven at 40 °C for 2 h.

2.3.3. HPMC sub-coated EUDRAGIT® L 30 D-55 coating

A standard EUDRAGIT® L 30 D-55 coating was applied on top of a HPMC sub-layer. Hydrophilic polymer sub-coatings, such as HPMC, are commonly applied beneath enteric coatings to prevent the degradation of acid-labile drugs by the acidity of the enteric

polymer. It was used in this study to compare the dissolution process to the EUDRAGIT® L 30 D-55 double coating system. The HPMC sub-layer formulation was prepared by dissolving 10% (w/w) HPMC in water. The outer coat formulation was identical to the single coating. The coating conditions for both the inner and outer coat were the same as for the single coating. Pellets were cured in an oven at 40 °C for 2 h after applying the outer coat.

The polymer amounts applied for the inner HPMC sub-coating and the outer EUDRAGIT® L 30 D-55 coating were 3 and 5 mg/cm^2 respectively. Preliminary studies revealed that a 3 mg/cm^2 inner layer of HPMC provided faster release than a 5 mg/cm^2 inner layer (data not shown). Since the EUDRAGIT® L 30 D-55 double-coating was found to accelerate drug release, to better compare to this effect, 3 mg/cm^2 polymer was applied for the HPMC inner coat.

2.4. In vitro drug release tests

Drug release from the coated prednisolone pellets was assessed using USP II paddle apparatus (Model PTWS, Pharma Test, Hainburg, Germany). The tests were conducted at least in triplicate, in 900 ml dissolution medium maintained at 37 ± 0.5 °C. A paddle speed of 50 rpm was employed. The tests were conducted under sink conditions. The amount of prednisolone released from the coated pellets was determined at 5 min intervals by an in-line UV spectrophotometer at a wavelength of 247 nm. Data were processed using Icalis software (Icalis Data Systems Ltd., Berkshire, UK). Pellets were placed for 2 h into 0.1 M HCl, and subsequently into pH 5.5 phosphate buffer (0.067 M, buffer capacity of 6.5 mM/L/pH unit) which reflects the luminal pH condition and buffer capacity of the proximal small intestine (Bratten and Jones, 2006; Kalantzi et al., 2006).

2.5. Confocal laser scanning microscopy (CLSM) testing

Pellets coated with the single coating, EUDRAGIT® L 30 D-55 double coating and HPMC sub-coating formulations were subjected to dissolution testing conditions and were removed at different time points to conduct the CLSM tests. The coating formulations used in this test contained fluorescent probes: 2% rhodamine B (w/w, based on dry polymer weight) was dissolved into the inner coat of the EUDRAGIT® L 30 D-55 double coating and HPMC sub-coating formulations; 1% fluorescein (w/w, based on dry polymer weight) was dissolved into the single coating and the outer coat of the EUDRAGIT® L 30 D-55 double-coated and HPMC sub-coated formulations. The inclusion of the probes into the inner or outer coat was based on their aqueous solubility. Rhodamine B which is very soluble in water (O'Neil et al., 2006) was included in the water soluble inner coat, whereas, fluorescein was added into the enteric outer coat because it is insoluble in the acidic condition of the outer coat formulation and thus would not alter the dissolution properties of the coat.

Dissolution of coated pellets for confocal testing was carried out in a dark room using USP II paddle apparatus (Model 85T-M, G. B. Caleva Ltd., Dorset, UK). To prevent the agglomeration of pellets during dissolution testing, a net device (round, diameter 8 cm) with 20 chambers (round, diameter 1 cm) having a 250 μm supporting mesh at the bottom was designed and used. Twenty pellets, one in each chamber, were placed into the net device and put into the bottom of the dissolution vessel with 900 ml of medium maintained at 37 ± 0.5 °C. The pellets were subjected to 0.1 M HCl for 2 h and subsequently pH 5.5 phosphate buffer (0.067 M). The distance between the paddle and the bottom of the chamber was adjusted to 25 ± 2 mm and a paddle speed of 50 rpm was applied. Pellets were removed from the media at predetermined time points (different pellets were used for each time point).

After the dissolution test pellets were dried at room temperature and cut in half and examined using CLSM. A Zeiss LSM 510 META Laser Scanning Confocal Microscope (Zeiss, Jena, Germany), equipped with a Plan-Neofluer 5×/0.15 air lens was applied. An Argon laser with 488 nm line and a Helium-Neon laser with 543 nm line were used. Images were stored as 1024 × 1024 pixel boxes (12-bit resolution).

2.6. Scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX)

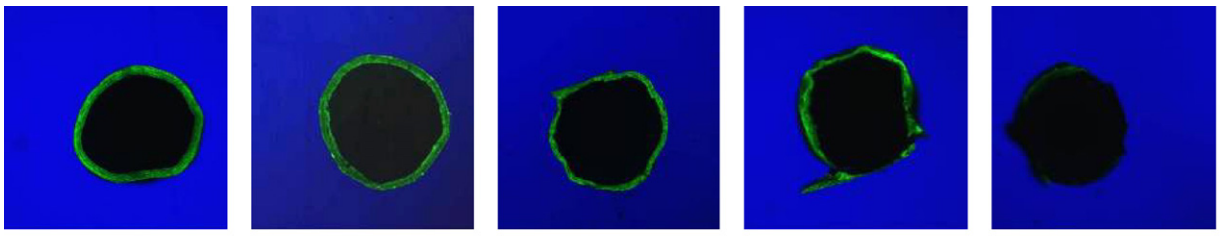
Sodium was chosen as a representative ion to illustrate the migration of ions from the inner coat to the outer coat of the EUDRAGIT® L 30 D-55 double coating system. Originally, this ion is only present in the inner coat due to the neutralisation of the coating formulation using 1 M NaOH during the preparation procedure. The distribution of sodium throughout the double coating during the dissolution process was examined using SEM/EDX. Pellets coated with the double coating formulation were placed in the same net device and subjected to the same dissolution process as for CLSM tests. Pellet samples removed from the dissolution medium were dried in an oven at 40 °C and cut in half. The cross-sections of the double coated pellets were examined by SEM using a JEOL JSM-840A Scanning Microscope (JEOL GmbH, Eching, Germany). Sodium distribution through the cross-section of the film coat of the double-coated pellets was examined using an EDX detector (model OXFORD INCA 200, Oxford Instruments Germany, Wiesbaden, Germany). The EDX detector is equipped with a liquid nitrogen cooled X-ray detector (Si(Li) – silicon with lithium) having 10 mm^2 crystal area. The working distance for the EDX detector was 15 ± 1 mm and the electron energy (acceleration voltage) was 15 keV. All samples for EDX testing were coated with carbon (~30–40 nm). EDX mapping was carried out by dividing the SEM picture of the cross-section of the film coat into 512 × 384 points and a spatial distribution of sodium was obtained (using the INCA software).

2.7. Influence of inner coat osmotic pressure on drug release from the EUDRAGIT® L 30 D-55 double-coated formulation

To assess the influence of inner coat osmotic pressure, drug release from the double-coated formulation was determined at different medium osmotic pressures. The osmotic pressure of the inner coat after 2 h acid exposure was determined. This was considered as the initial inner coat osmotic pressure in buffer and was used to design an osmotic pressure gradient between the inner coat and the external medium. This was conducted by measuring the amount of acid taken up by the inner coat and thus calculating the concentration of dissolved adipic acid in the inner coat. The osmotic pressure of the adipic acid solution at the same concentration was determined and considered as the inner coat osmotic pressure.

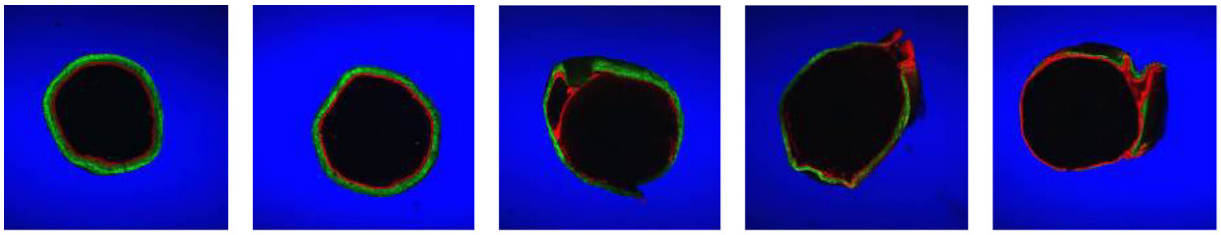
Coated glass beads were used to determine the acid uptake of the coats due to the elimination of the influence of the core material. Glass beads were coated with the double coating formulation (15% adipic acid) and the single coating formulation following the methods described in Section 2.3.2 and 2.3.1 respectively. Ten coated glass beads of each formulation were weighed and subjected to dissolution conditions in 0.1 M HCl using the net device described in Section 2.5. After 2 h the beads were removed and excess medium was drained and blotted with filter paper from the surface of the beads. The beads were weighed again and the acid uptake by the double coating and the single coating was calculated. The amount of acid taken up by the inner coat was the deduction of the acid uptake of the double coating and the single coating.

The concentration of the dissolved adipic acid in the inner coat after acid treatment was calculated based on the acid uptake. Adipic



(A) Before acid treatment (B) After acid treatment (C) **80 minutes** in buffer (D) **110 minutes** in buffer (E) **140 minutes** in buffer

Fig. 2. Confocal images of the EUDRAGIT® L 30 D-55 single layer coated pellets.



(A) Before acid treatment (B) After acid treatment (C) **60 minutes** in buffer (D) **90 minutes** in buffer (E) **110 minutes** in buffer

Fig. 3. Confocal images of the EUDRAGIT® L 30 D-55 coated pellets with an HPMC sub-layer.

acid solution at the above concentration (neutralised to the same pH as the inner coat formulation, pH 5.6, using 1 M NaOH) was prepared. The osmotic pressure of the solution was measured to represent the osmotic pressure of the inner coat, using an osmometer (Hermann Roebling MESSTECHNIK, Berlin, Germany).

Urea was used as the osmotic agent to increase the osmotic pressure of the dissolution medium. Drug release studies of the double coated prednisolone pellets were performed in pH 5.5 phosphate buffer containing 0, 0.5, 1 and 2 M urea using the dissolution testing method described in Section 2.4. The osmotic pressures of these dissolution media were measured.

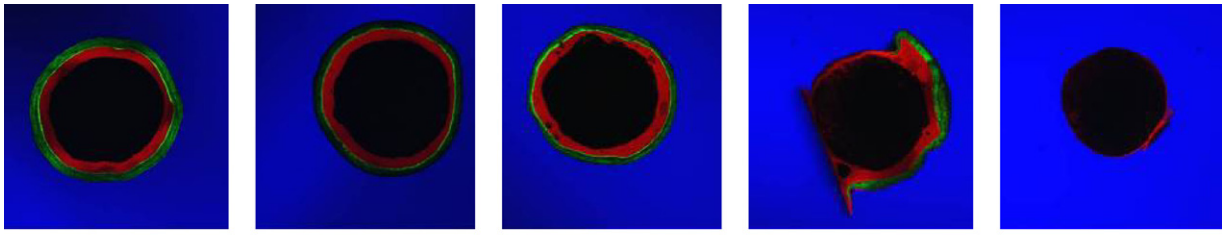
3. Results and discussion

3.1. Coating dissolution processes by CLSM

The coat dissolution of the EUDRAGIT® L 30 D-55 double-coating was compared with a conventional single enteric coating and a HPMC sub-coated enteric system using CLSM (Figs. 2–4). The single coating showed no change after 2 h pre-treatment in 0.1 M HCl (Fig. 2). The coat dissolved slowly from the pellet core in pH 5.5 phosphate buffer. The confocal images show that the coat dissolution started after 80 min in buffer. The rupture of the coat can be seen at 110 min, and the coat completely dissolved at 140 min.

For the EUDRAGIT® L 30 D-55 formulation with an HPMC sub-layer, no difference was seen before and after 2 h acid treatment (Fig. 3). After exposure to pH 5.5 buffer for 60 min, holes were seen in the inner HPMC layer. This is attributed to the penetration of buffer solution through the outer coat and the subsequent swelling of the HPMC inner layer, which caused then an earlier rupture of the outer coat (90 min) compared to the single coating. Complete outer coat dissolution occurred at 110 min for the HPMC sub-coated formulation.

The inner and outer coats of the novel EUDRAGIT® L 30 D-55 double-coating system also remained intact after 2 h acid treatment (Fig. 4). This indicates good acid resistance of the double-coating system on pellets and is in agreement with previous results when applied on tablets (Liu et al., 2009). In pH 5.5 buffer, in contrast to the slow dissolution of the above two formulations, the double coating dissolved much faster. After 35 min in buffer, there were large pores in the inner coat, while the outer coat remained intact. The buffer medium penetrated the outer coat and came into contact with the inner coat. Since the inner EUDRAGIT® L 30 D-55 polymer has been converted to a water soluble polymer by neutralisation during the preparation process, the inner coat dissolved quickly upon contact with the influx buffer solution. In contrast to the HPMC sub-coating, it was not the swelling of the inner layer that was responsible for the rupture of the outer coat; the dissolution of the outer coat was accelerated by the dissolved inner coat. The outer coat dissolved rapidly and ruptured after 45 min in pH 5.5 buffer. After 55 min, both the inner and outer coat dissolved completely from the pellet core.



(A) Before acid treatment (B) After acid treatment (C) **35 minutes** in buffer (D) **45 minutes** in buffer (E) **55 minutes** in buffer

Fig. 4. Confocal images of the EUDRAGIT® L 30 D-55 double-coated pellets.

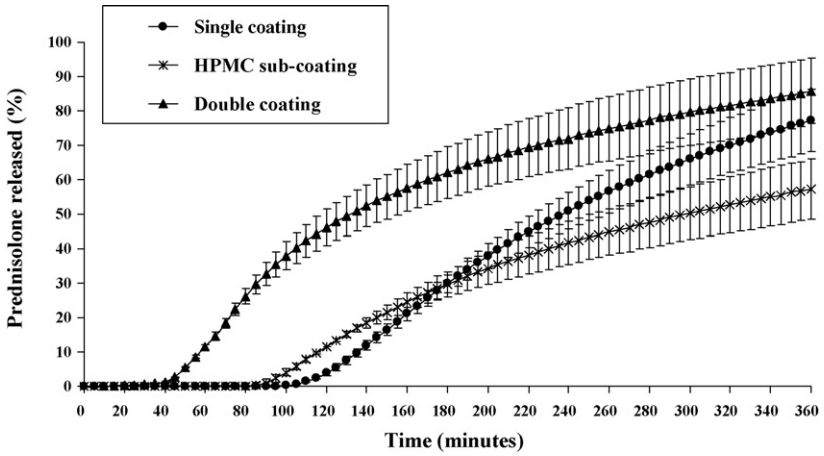


Fig. 5. Drug release profiles of the EUDRAGIT® L 30 D-55 single-coated, HPMC sub-coated and double-coated prednisolone pellets in pH 5.5 phosphate buffer after pre-treatment in 0.1 M HCl for 2 h.

These three formulations showed no drug release in 0.1 M HCl for 2 h (data not shown). In subsequent pH 5.5 buffer, the drug release lag times for the single-coated, HPMC sub-coated and EUDRAGIT® L 30 D-55 double-coated pellets were 105, 90 and 40 min respectively (Fig. 5). These lag times correlate well with the outer coat rupture times obtained from the CLSM analysis. The rapid dissolution of the double-coating system led to an earlier rupture of the coat, shorter lag time and faster drug release rate compared to the single-coated and HPMC sub-coated systems. The drug release rate from the HPMC sub-coated pellets was slower compared to the single-coated pellets after the lag time. This can be attributed to an increased micro-environmental viscosity surrounding the pellets caused by the dissolution of the HPMC inner layer.

3.2. Coating dissolution process of the EUDRAGIT® L 30 D-55 double coating by SEM/EDX

It was hypothesized that the water soluble components in the inner coat of the double-coating, such as organic acid and its sodium salt (formed due to the addition of 1 M NaOH) can migrate into the outer coat during the dissolution process, thus assisting in its dissolution. This migration was investigated through SEM/EDX tests using sodium as a representative ion. These tests were not applied to the single coating and the HPMC sub-coating due to the absence of sodium in these systems.

Fig. 6 shows the physical changes of the coat and the sodium distribution throughout the double coating after removal from pH 5.5 phosphate buffer at different time points. The coating dissolution process revealed by SEM correlate well with those obtained from the CLSM tests. EDX images show that sodium was first concentrated in the inner coat and migrated toward the outer coat during dissolution. After 50 min in buffer, sodium was distributed homogeneously throughout the whole double coating.

3.3. Mechanisms involved in the dissolution of the EUDRAGIT® L 30 D-55 double coating system

Due to the presence of salts in the inner coat of the double coating, the osmotic pressure of the inner coat was increased. To investigate the role of inner coat osmotic pressure on the dou-

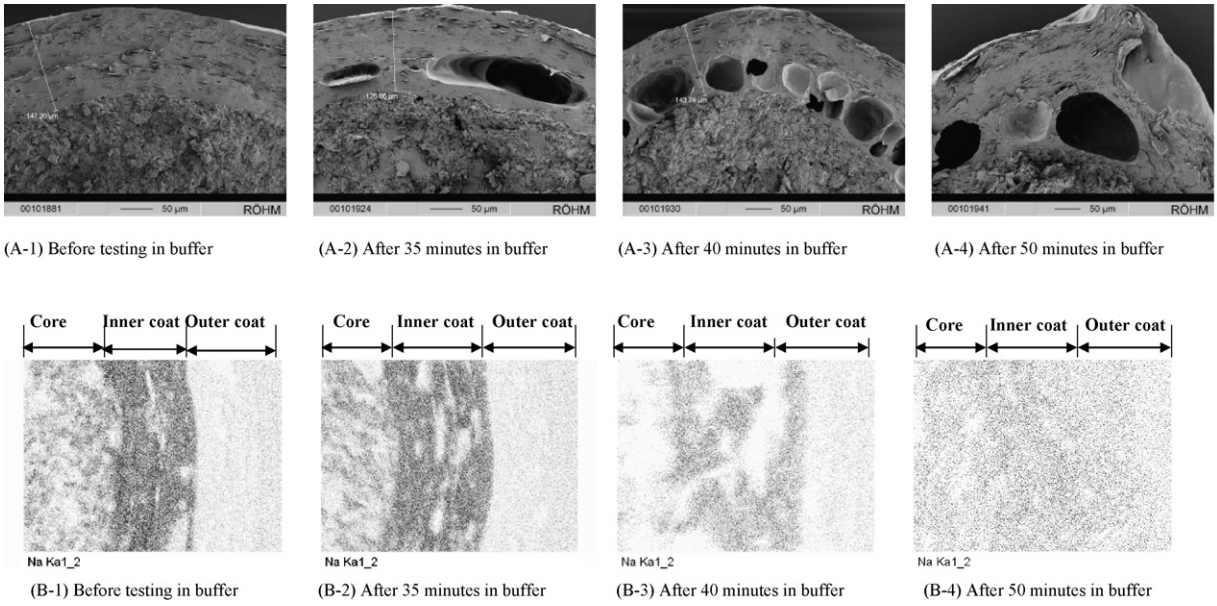


Fig. 6. Scanning electron micrographs (A-1–A-4) and EDX images (B-1–B-4) of the EUDRAGIT® L 30 D-55 double-coated pellets at different time points in pH 5.5 phosphate buffer. The black dots in the EDX images represent sodium ions.

ble coating dissolution, dissolution tests for the double-coated prednisolone pellets were conducted in pH 5.5 phosphate buffer with different osmotic pressures (achieved by adding different concentrations of urea). The acid uptake of the inner coat after exposure to 0.1 M HCl for 2 h was 3.45×10^{-3} ml/cm^2 (the amount of acid in the film coat). This gave the dissolved adipic acid concentration in the inner coat of 43.3 mg/ml and an osmotic pressure of 2124 mOsmo/kg H_2O at pH 5.6 (the pH of the inner coat formulation). The osmotic pressure gradients between the inner coat and the dissolution medium were 2005, 1520, 1072 and −153 mOsmo/kg H_2O for the 0, 0.5, 1 and 2 M urea concentration. Drug release was the same at the different medium osmotic pressures (data not shown), indicating that the inner coat osmotic pressure did not contribute to the rapid dissolution of the double coating system.

Apart from the osmotic pressure, the ionic strength and buffer capacity of the inner coat were also increased related to the presence of acids and salts. Effects of ionic strength and buffer capacity on the dissolution of acidic polymers have been reported in the literature (Shek, 1978; Spitael et al., 1980; Ozturk et al., 1988a; Kararli et al., 1995; Fadda and Basit, 2005; Ibekwe et al., 2006, 2008; Fadda et al., 2008). Spitael and Kinget (1977) explained the influence of ionic strength on the dissolution of anionic polymers by applying general base catalysis. The anionic polymers dissolve through the dissociation of the carboxylic acid groups by proton transfer to water molecules. A general base makes the proton transfer easier by activating the oxygen atom of the water molecule with extra electrons by pulling a proton from it (Bender and Brubacher, 1973). The buffer capacity of the medium influences the anionic polymer dissolution by affecting the microenvironment pH adjacent to the dissolving polymer which can be 0.2–0.6 units lower than the bulk pH, due to the generation of protons at the surface of the dissolving polymer (Ozturk et al., 1988b; Harianawala et al., 2002). In a buffered medium, this pH decrease is suppressed by the ability of the buffer salt to absorb protons depending on its buffer capacity.

In the case of the double coating system, upon exposure to the influx buffer medium, the increased ionic strength of the dissolved inner coat assisted the dissolution of the outer coat from the inner surface. After the outer coat starts to dissolve, the acidity of the polymer would be expected to decrease the pH inside the coat. The buffer capacity of the inner coat then starts to play an important role to suppress this decrease and maintain the crucial pH for the outer coat to dissolve.

3.4. Influence of media on the dissolution of the EUDRAGIT® L 30 D-55 double-coating system

The rapid dissolution of the outer coat of the double coating is the result of two parallel processes. The first process is the penetration of buffer medium through the outer coat into the inner coat, resulting in the fast dissolution of the water soluble inner coat. The dissolved organic acids and salts in the inner coat then start to migrate toward the outer coat. With the assistance of these acids and salts, the outer EUDRAGIT® L 30 D-55 coat starts to dissolve from its inner surface. The second process is the dissolution of the outer coat from the outer surface in contact with the external buffer medium. Fig. 7 illustrates the changes in the outer coat during these dissolution processes.

The significance of the first process on the dissolution of the double-coating system depends on the properties of the dissolution medium. At any time during the dissolution process the remaining film thickness l_f can be given by Eq. (1) (the definition of the film thickness was provided in Fig. 7):

$$l_f = l_o - l_{d1} - l_{d2} \quad (1)$$

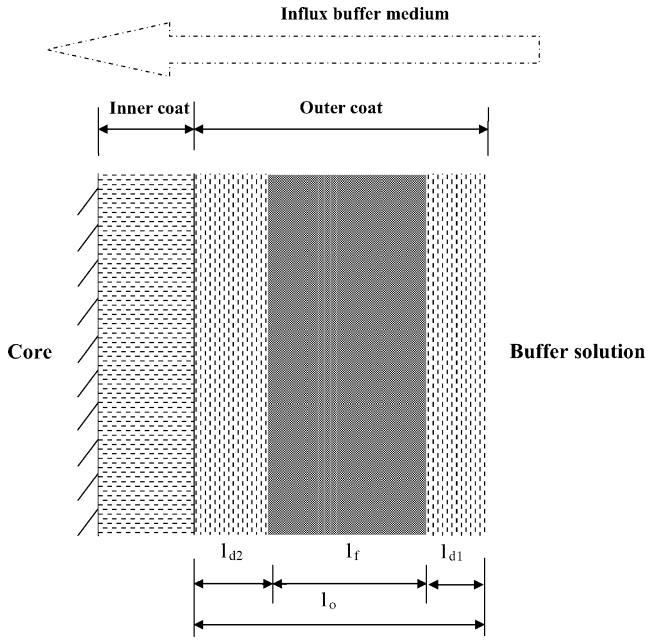


Fig. 7. Schematic representation of the outer coat dissolution process of the double-coating system: the initial physical film thickness, l_o; the thickness of film dissolved from the outer surface, l_{d1}; the thickness of film dissolved from the inner surface, l_{d2}; and the instantaneous physical film thickness, l_f. (The inner and outer coat in this figure do not reflect their actual thicknesses.)

Therefore, the rate of change of the remaining film thickness, dl_f/dt, is determined by the rates of dl_{d1}/dt and dl_{d2}/dt. The properties of the dissolution media, such as pH, ionic strength and buffer capacity, affects the rate of film dissolution from the outer surface, dl_{d1}/dt. Taking the medium pH as an example, dl_{d1}/dt is low at low pH. Therefore, dl_{d2}/dt is the dominant factor determining the whole process of the outer coat dissolution. However, when the medium pH elevates, dl_{d1}/dt increases; consequently, the significance of dl_{d2}/dt on the dissolution process of the double-coated system reduces.

4. Conclusions

The EUDRAGIT® L 30 D-55 double coating is acid-resistant and markedly accelerated the coating dissolution in simulated upper small intestinal conditions relative to conventional enteric systems. The dissolution mechanism of the double coating system was unusual. Unlike the HPMC sub-coated enteric formulation in which the swelling of the sub-layer led to the rupture of the outer coat, the rapid dissolution of the double coating system was due to the dissolution of the outer coat from both the inner surface and outer surface. The dissolution of the outer coat from the inner surface was attributable to the increased ionic strength and buffer capacity of the inner coat and the migration of water soluble components from the inner to the outer coat.

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