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Colonic release and reduced intestinal tissue damage of coated tablets containing naproxen inclusion complex

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Abstract

A colonic-release delivery system containing naproxen inclusion complex with 2-hydroxypropyl-β-cyclodextrin (2-HPβCD) was originally proposed. The core tablets consisting of the naproxen inclusion complex and disintegrants (Ac-Di-Sol®, Primojel®, Avicel® or Polyplasdone®) were formed by direct compression, and then coated with the polymers, either pH-dependent Eudragit® S100 and/or pH-independent Eudragit® RS100 with plasticizers like dibutyl sebacate (DBS) and aluminum tristearate (AT). The *in vitro* release characteristics were evaluated in simulated gastric fluid for 2 h and then subsequently in simulated intestinal fluid for 12 h. The potential histological changes were also evaluated after direct dosing of suspensions of naproxen alone and powdered mixtures of inclusion complex-loaded tablet into rat intestinal segments. No distinct colonic release was observed when disintegrants were excluded in the single-layered coated tablets regardless of coated structures, giving a zero-order fashion over 12 h. The coated tablet with double-layered structures of Eudragit® S100 and Eudragit® RS100 was not also applicable. In contrast, colonic release was achieved when the core tablet containing inclusion complex and disintegrant was coated with only Eudragit® S100 in a single-layered structure. The colonic-release tablet was resistant in gastric fluid for 2 h and for 2–4 h in intestinal fluid, followed by rapid release of the drug after a total of 4–6 h of lag time depending on the type of disintegrants. The lag time was advanced in case of DBS while delayed in case of AT. On histological examination, the inclusion complex-loaded suspension caused less intestinal tissue damage than naproxen alone. Based on these findings, the colonic-release tablet with enteric coatings which contains inclusion complex and disintegrants could be useful to deliver drugs like naproxen to the lower small intestine and upper colon with increased dissolution and reduced intestinal tissue damage.

Keywords: Naproxen; Inclusion complex; Colonic release; Different coated structures; Reduced intestinal tissue damage

1. Introduction

Naproxen is a potent and commercially available NSAID that is used to treat rheumatoid arthritis, osteoarthritis and colitis (Espinar et al., 1991). There have been some trials to deliver naproxen to the lower intestine and upper colon to treat intestinal diseases such as colitis and Crohn's disease (Larsen et al., 1989; Rao et al., 2003). However, delivery of naproxen was limited because of its poor water solubility and undesirable gastrointestinal toxicity such as gastrointestinal intolerance and ulceration when given orally (Espinar et al., 1991; Rodríguez, 1997). So far, no distinct delivery system is investigated to release naproxen in a controlled manner at the proximal site or colon to overcome these problems.

Cyclodextrin and its derivatives have played a very important role in the formulation of poorly water-soluble drugs like naproxen by improving apparent drug solubility, stability and bioavailability (Lee and Lee, 1995; Mura et al., 2003). Furthermore, drug inclusion complexes with ß-cyclodextrin and its derivatives are also known to have little direct contact with the gastrointestinal tract, resulting in less irritation and toxicity of drugs (Espinar et al., 1991; Rodríguez, 1997). Among several cyclodextrin derivatives, 2-hydroxypropyl-β-cyclodextrin (2-HPβCD) has drawn attention because of its higher water solubility compared to other derivatives (Lee and Lee, 1995; Mura et al., 2003).

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Colonic drug delivery has also gained increasing importance not just for delivery of drugs to treat local diseases, but also for its potential to deliver proteins and therapeutic peptides (Rao et al., 2003; Rubinstein, 2005). To achieve successful colonic delivery, a drug needs to be protected from absorption and the environment of the upper gastrointestinal region and then be promptly released into the proximal colon, which suggests colonic-release system can be desirable. In general, colonic-release drug delivery systems are characterized by two release phases: the first phase in which little or no drug is released is called the lag time and is followed by the second phase in which the drug is completely released over a short period of time. One of conventional methods to delay the release of drugs for colonic delivery is to coat the dosage forms with pH-dependent polymeric materials like Eudragit® S100 (Ashford et al., 1993; Chourasia and Jain, 2004; Rubinstein, 2005) The lag time of the colonic drug delivery system can be controlled by the composition and type of coating material as well as by the thickness (weight) and layer structure of the coated films. The polymeric film coatings have been also used in the development of various controlled-release dosage forms (Lee et al., 1999; Kim et al., 2007a, 2007b).

Based on the poor solubility and potential tissue damages of drug as well as its clinical applications to treat inflammatory bowel diseases, a colonic-release tablet containing inclusion complex of naproxen followed by polymeric coatings would be of particular interest to reduce potential in vivo intestinal tissue damages and to improve dissolution when exposed to proximal intestinal sites or colon.

The aim of this study was focused on the development of colonic-release tablet containing naproxen inclusion complex with 2-HPβCD to deliver the drug into colonic region and also to reduce gastrointestinal tissue damage by naproxen itself. To achieve colonic release, various tablet formulations were designed varying type of disintegrants (Ac-Di-Sol®, Primojel®, Avicel® or Polyplasdone®) in core tablet, coating polymers (pH dependent Eudragit® S100 and/or pH independent RS100) with or without plasticizers (DBS or AT), and coating layer structures. Release profiles of the tablets were extensively investigated in simulated gastric fluid for 2 h followed by intestinal fluids. Histological changes of potential intestinal tissue damages were also evaluated after direct dosing of naproxen suspension or naproxen-inclusion complex-loaded tablet suspension into rat intestinal segments.

2. Materials and methods

2.1. Materials

Naproxen powder, cross-linked carboxymethylcellulose sodium (Ac-Di-Sol®), sodium starch glycolate (Primojel®), microcrystalline cellulose (Avicel®) and crospovidone (Polyplasdone®) were kindly provided as a courtesy of Chong-Kun Dang (Seoul, Korea). 2-HPβCD was obtained from Richwood (Seoul, Korea). The average molecular weight and molar substitution of 2-HPβCD were 1500 and 0.8, respectively. Eudragit® S100 and Eudragit® RS100 were provided as a courtesy of Degussa (Seoul, Korea). Dibutyl sebacic acid (DBS) was purchased from Sigma (St. Louis, MO). Talc, a purified and hydrated magnesium silicate, was purchased from Showa (Japan). Magnesium stearate and aluminum tristearate (AT) were purchased from Katayama (Osaka, Japan). Ammonium hydroxide (NH_4OH) was obtained from Duksan (Seoul, Korea). All other chemicals were reagent grade and used without further purification.

2.2. Preparation of naproxen inclusion complex

The naproxen inclusion complex was prepared by the kneading method as reported previously (Lee and Lee, 1995). In detail, 0.6 g naproxen and 3.91 g 2-HPβCD at an equimolar ratio were mixed in a mortar with a pestle to form a paste with the dropwise addition of 10 mL ethanol. The paste was dried in an oven at 50 °C for 24 h. The inclusion complex was stored in a desiccator until use.

To determine the naproxen content of inclusion complex, 1000 mg of inclusion complex was added in 500 ml of ethanol. After sonication for 5 min, the concentration of naproxen was measured by an UV–vis spectrophotometer at the wavelength of 271 nm with proper dilution. The total naproxen content in the inclusion complex was estimated to be 9.8% (w/w).

2.3. Preparation of core tablets

The core tablet compositions based on weight are shown in Table 1. The inclusion complex (94%) was blended with 4% disintegrant (Ac-Di-Sol®, Primojel®, Avicel® or Polyplasdone®), and subsequently mixed with 1% talc and 1% magnesium stearate. The resulting powder mixtures were directly com-

Table 1
Core tablet compositions

Core	IC[a] (%)	Talc (%)	Magnesium stearate (%)	Disintegrant			
				Ac-Di-Sol (%)	Primojel (%)	Avicel (%)	Polyplasdone (%)
F0	98	1	1	–	–	–	–
F1	94	1	1	4	–	–	–
F2	94	1	1	–	4	–	–
F3	94	1	1	–	–	4	–
F4	94	1	1	–	–	–	4

[a] Inclusion complex.

Table 2
Formulation compositions of coating solutions

Codes	Core	Coating solution		
F0 S100	F0	Eudragit® S100	–	–
F0S100RS100[a]	F0	Eudragit® S100	Eudragit® RS100	–
F0S100RS100/DBS[a]	F0	Eudragit® S100	Eudragit® RS100	DBS
F1S100	F1	Eudragit® S100	–	–
F2S100	F2	Eudragit® S100	–	–
F3S100	F3	Eudragit® S100	–	–
F4S100	F4	Eudragit® S100	–	–
F2S100/DBS	F2	Eudragit® S100	–	DBS
F2S100/AT	F2	Eudragit® S100	–	AT
F2S100RS100[a]	F2	Eudragit® S100	Eudragit® RS100	–
F2S100/RS100[b]	F2	Eudragit® S100	Eudragit® RS100	–

[a] Double-layered coating.
[b] Mixed solution of Eudragit® S100 and Eudragit® RS100 (3:1, w/w ratio).

pressed in a rotary tablet press (Korea Machine, Seoul, Korea) equipped with pillow-faced punches. The tablet dimension was estimated as 6.0 ± 0.1 mm in thickness and 9.0 mm in diameter. The mean tablet weight and hardness of 30 core tablets were 300 ± 10 mg and 100.0 ± 20.0 N, respectively.

2.4. Preparation of coated tablets

Compositions of the polymeric coating solutions are given in Table 2. Eudragit® S100 (16 g) or Eudragit® RS100 (16 g) was dissolved in 200 ml of acetone and ethanol (7:3, v/v). Thereafter, talc and/or 20% (v/v) plasticizer (DBS or AT) was added based on polymeric solid contents and the mixture was stirred for 24 h to ensure sufficient plasticization of the polymer and to get homogeneous solution.

The polymeric coating solution was manually sprayed onto the surface of the core tablet and then dried the solvents with a hand-drier. The tablet turned over to make coating of the other sides. The single-layered coated tablet was completely dried. Then the coating process using different polymeric solution was continuously repeated to get the double-layered coatings. The same solvents were used also for the second coating process. The first layer was not solubilized during the second coating step because the coating process by spraying polymeric solution followed by drying was instantaneously occurred.

This coating steps were repeated to make double-layered coated tablets until 10% weight gains were achieved compared to uncoated core tablet. The coating level was designated as the percentage of weight gained compared with uncoated tablets. Depending on the composition of coating solution and coating order, the single- or double-layered coated film could be obtained. Fig. 1 shows the coated structures of colonic-release tablet.

2.5. Disintegration of core tablets

Disintegrating time was measured in distilled water, simulated gastric and gastric and intestinal fluid at 37 ± 0.5 °C, according to the method described by the Korean Pharmacopoeia (KP VIII) disintegration test using a tablet disintegration tester (Labfine Inc., Seoul, Korea). The tablets were considered completely disintegrated when all particles passed through the wire mesh.

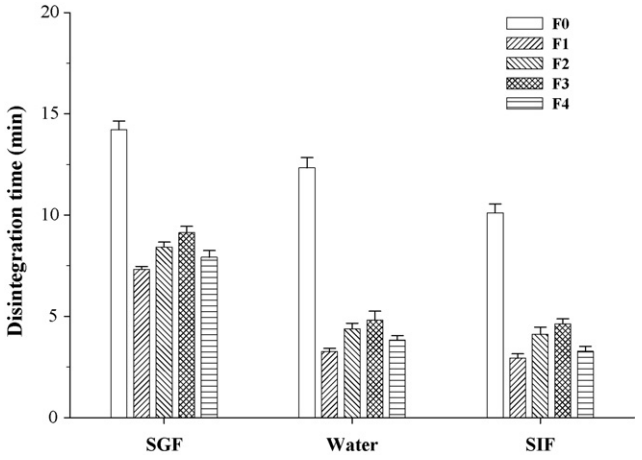

Fig. 1. Comparison of disintegration time of core tablet naproxen containing inclusion complex in water, gastric and intestinal fluid.

2.6. Release studies

Release studies were performed in pH 1.2 simulated gastric fluid for 2 h and subsequently in pH 6.8 simulated intestinal fluid for 12 h with the standard paddle method. The simulated gastric fluid was prepared by dissolving NaCl (6 g) in about 2900 ml of deionized water and then diluted HCl (7.4%) was added to adjust pH 1.2 ± 0.1. The simulated intestinal fluid was also prepared as follows. Potassium phosphate monobasic (20.4 g, KH_2PO_4) was dissolved in about 2800 ml of deionized water and then NaOH (1N) was added to adjust pH 6.8 ± 0.1. The final volume was adjusted to 3000 ml using deionized water.

The test was performed in triplicate using dissolution apparatus II (Fine Scientific DST600A, Seoul, Korea) at 37 ± 0.5 °C with a stirring speed of 50 rpm. Tablets containing naproxen inclusion complex were placed in 500 ml of simulated gastric (pH 1.2 ± 0.1) fluid for 2 h, and then continuously in 500 mL of simulated intestinal (pH 6.8 ± 0.1) fluid. Three millilitres of dissolution media were collected at given time intervals and replaced with an equal volume of temperature-equilibrated media. The collected media was filtered through 0.45 μm membrane, and the concentration of dissolved drug was measured using an UV–vis spectrophotometer at a wavelength of 271 nm.

2.7. Histological evaluation of rat intestinal tissue

Male Sprague–Dawley rats (250 g) were obtained from Dae-Han Animal Laboratory (Seoul, Korea). They were housed in a temperature-controlled room (25 ± 2 °C) with a 12/12-h light–dark cycle (light from 08:00 to 20:00) and allowed free access to food and tap water. After a 2-week acclimation period, the suspension of naproxen alone or powdered mixtures of tablet containing naproxen-inclusion complex was directly administered into each intestinal segment of three rats (duodenum, ileum, and colon) at a dose of 200 mg/kg naproxen using an injection needle. Thirty minutes after administration, the rats

were sacrificed, and each intestinal tissue was removed and fixed in formalin. For histological examination, the intestinal tissues were serially cross-sectioned at 5-μm thickness using a microtome and stained with Harris hematoxylin-eosin solution on glass slides. Histopathological examination was carried out at 40× magnification using an Olympus Bx microscope (Tokyo, Japan) linked with imaging software (Baumer Twain Ver. 1.0, Humin Tech Corp., Seoul) in the Central Laboratory, Kangwon National University.

3. Results and discussion

3.1. Release characteristics

Disintegrants possessing a weak acidic group such as carboxymethyl cellulose (Na form) (Ac-Di-Sol®) or starch glycolate (Na form) (Primojel®) swell completely different in pH 1.2 and 6.8, and the disintegrating time will be different in these fluids. Disintegration time of core tablet naproxen containing inclusion complex in water, gastric and intestinal fluid is compared in Fig. 1. The disintegration time was much slower in the gastric fluid followed by water and intestinal fluid in order. All core tablets completely disintegrated within 5 min in water and simulated intestinal fluid except the tablet without disintegrant (F0). Disintegration time of core tablet without adding disintegrant in water, gastric fluid and intestinal fluid was 12.3 ± 0.51, 14.2 ± 0.43 and 10.1 ± 0.44 min, respectively.

Tablet disintegration time was closely related to the initial disintegrating force of the disintegrants. The order of disintegration time was invariably Ac-Di-Sol® (F1) > Polyplasdone® (F4) > Primojel® (F2) ≥ Avicel® (F3) > no disintegrant (F0) in water, gastric and intestinal fluid. However, these disintegration forces could be more complicated when polymeric coatings was performed hereafter.

The release profiles of uncoated core tablets containing naproxen inclusion complex and various types of disintegrants are shown in Fig. 2. Naproxen is a weak acid ($pK_a = 4.2$) and poorly water-soluble but has greater solubility in alkaline solution than in acidic media, which causes pH-dependent solubility and release profiles (Mura et al., 2003). We previously proved that the solubility and release rate of naproxen increased by complexation with 2-HPβCD in simulated gastric and intestinal fluid as compared with naproxen alone (Lee and Lee, 1995). However, drug dissolution of core tablets containing inclusion complex did not occur in gastric fluid but increased rapidly in all core tablet formulations as it was brought into simulated intestinal fluid until it reached equilibrium. With Ac-Di-Sol®, the uncoated core tablet had the highest release in both simulated gastric and intestinal fluids compared to those with other disintegrants.

The effect of disintegrants on the release profiles of tablets coated with Eudragit® S100 is shown in Fig. 3. Because Eudragit® S100 is a pH-dependent anionic polymer that dissolves in aqueous media above pH 7, tablets coated with Eudragit® S100 were resistant to gastric fluid, but dissolved rapidly in intestinal fluid. The coated tablet (F0S100) without disintegrant demonstrated more sustained release for 12 h. In

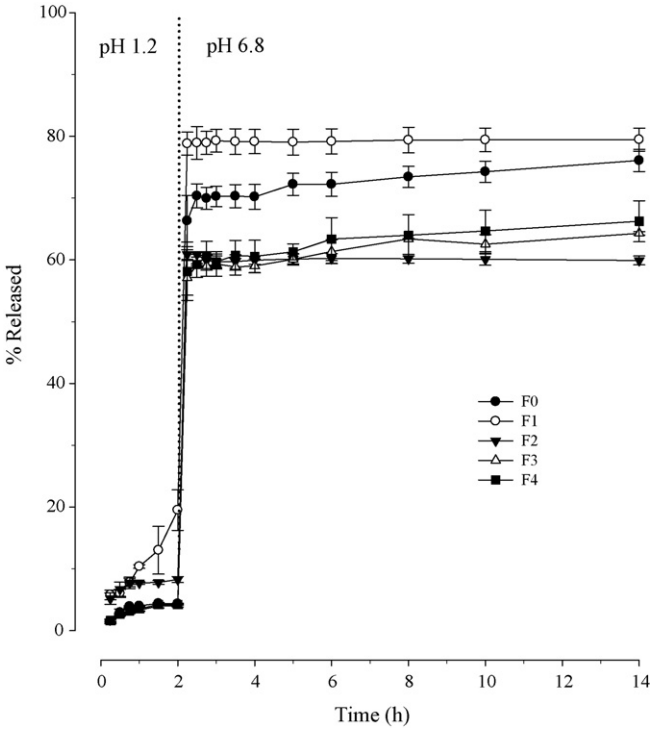

Fig. 2. Release profiles of uncoated core tablet containing naproxen inclusion complex with different types of disintegrants. F0 (no disintegrant); F1 (Ac-Di-Sol®); F2 (Primojel®); F3 (Avicel®); F4 (Polyplasdone®).

contrast, other Eudragit® S100-coated tablets containing disintegrants exhibited immediate release after the predetermined lag time, which was arbitrarily defined as the time period in which less than 10% of the drug was released. The lag time for

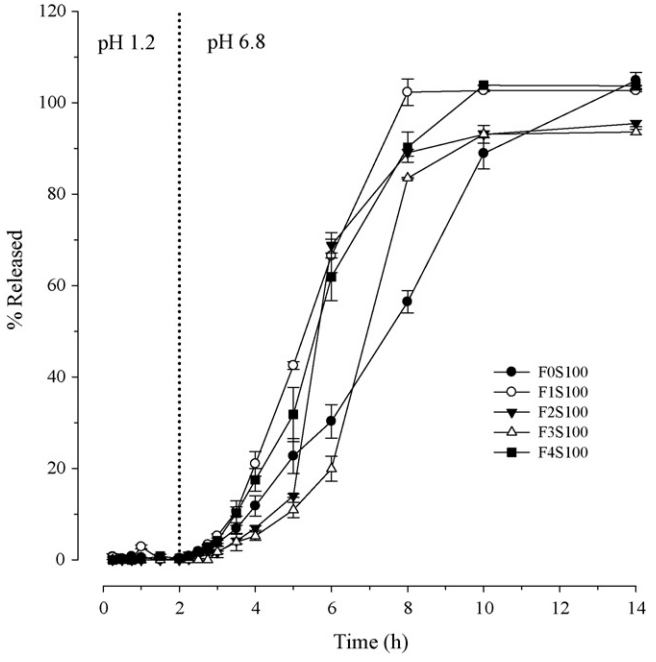

Fig. 3. The effect of disintegrants on release profiles of tablets coated with Eudragit® S100. F0 (no disintegrant); F1 (Ac-Di-Sol®); F2 (Primojel®); F3 (Avicel®).

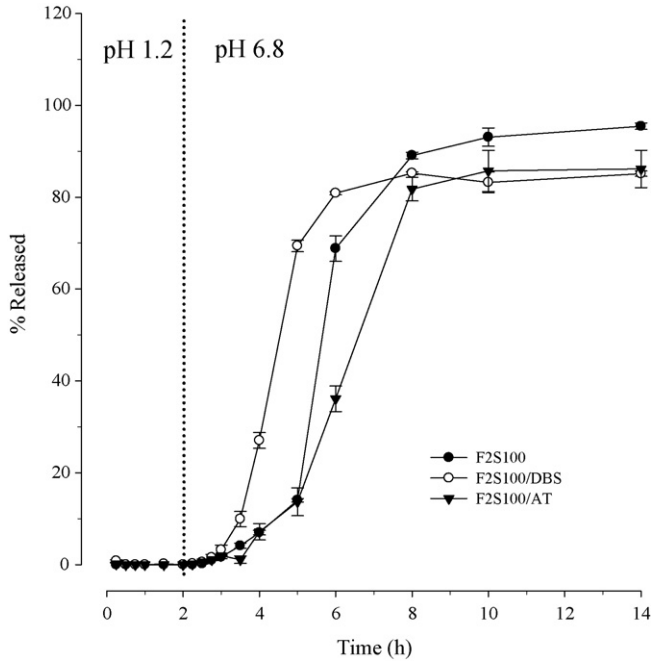

Fig. 4. The effect of plasticizers on the dissolution profiles of tablets coated with Eudragit® S100. F2S100 (no plasticizer); F2S100/DBS; F2S100/AT.

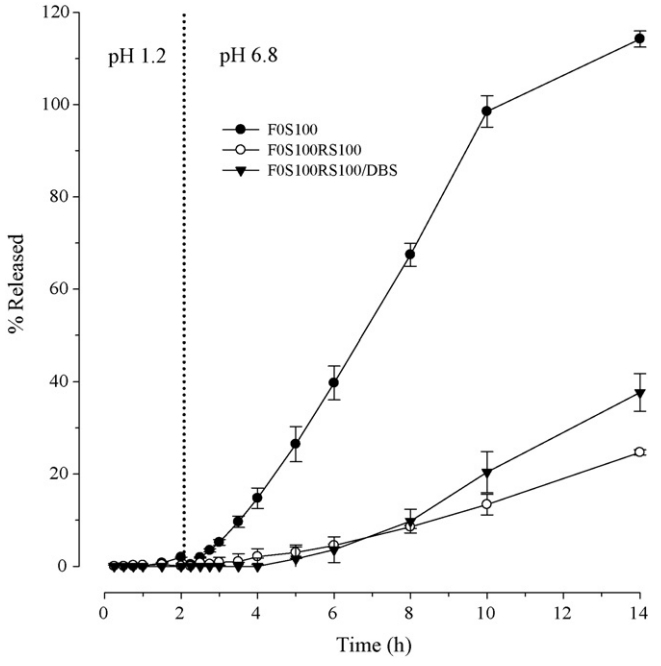

Fig. 5. The effects of coating layer structures on the release profiles of tablets excluding disintegrants. F0S100 (single-layered coating with Eudragit® S100); F0S100RS100 [double-layered coating with Eudragit® S100 (outer) and Eudragit® RS100 (inner)]; F0S100RS100/DBS [double-layered coating with Eudragit® S100 (outer) and Eudragit® RS100 containing DBS (inner)].

F1S100 (Ac-Di-Sol®) and F4S100 (Polyplasdone®) was about 4 h, and for F2S100 (Primojel®) and F3S100 (Avicel®) was 4.5 and 5 h, respectively. The F2S100 showed much steeper and faster release than other Eudragit® S100 coated tablets although the initial disintegration time of core tablet was a little slower (see Fig. 2).

Fig. 4 shows the effect of plasticizers on the release profiles of Eudragit® S100-coated tablets (F2S100). The release profiles were affected by plasticizers, and the changes were dependent on the type of plasticizer as discussed previously (Kim et al., 2007a). Hydrophobic DBS improved the release rate, while AT delayed the release. As a result, the lag time was 1 h shorter with DBS, but was longer with AT, compared to Eudragit® S100-coated tablets without plasticizer.

Release profiles are also known to be highly affected by the coating layer structure, in other words, by whether the coating was a single- or double-layer (Lee et al., 1999; Kim et al., 2007b). The effects of coating layer structures on the release profiles of tablets without disintegrants are given in Fig. 5. As mentioned previously, tablets coated with a single layer of Eudragit® S100 were resistant to gastric fluid, but exhibited retarded and sustained zero-order release in intestinal fluid for 12 h with no colonic release. When the core tablet was coated with double-layers of pH dependent Eudragit® S100 (outer layer) and pH independent Eudragit® RS100 (inner layer), the release rate was very low and was further retarded over 14 h. No distinct colonic release was observed over 14 h with double-layered coatings. DBS slightly increased the release rate, but the desired colonic release was not achieved by single- and double-layered coatings when disintegrants were excluded.

As shown in Fig. 6, the effects of coating layer structures on the colonic-release profiles were more pronounced in

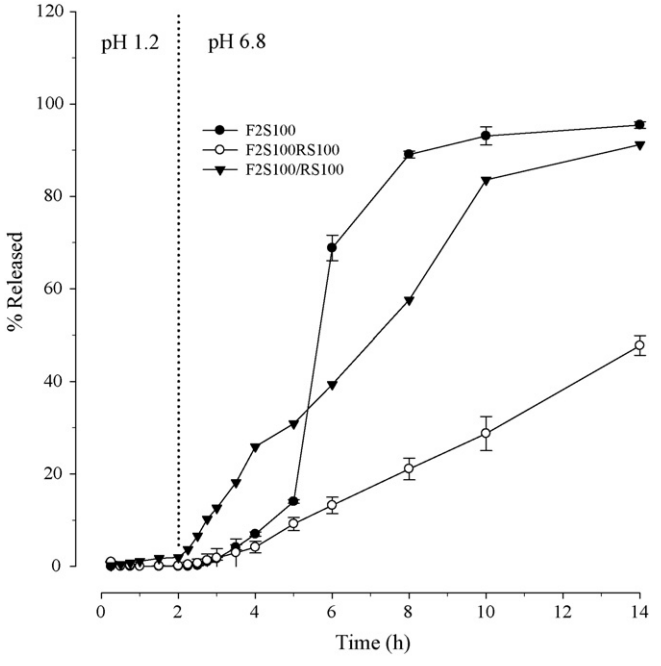

Fig. 6. The effect of coating layer structures on the release profiles of tablets including disintegrant. F2S100 (single-layered coating with Eudragit® S100); F2S100RS100 [double-layered coating with Eudragit® S100 (outer layer) and Eudragit® RS100 (inner layer)], F2S100/RS100 [single-layered coating with mixed solution of Eudragit® S100 and Eudragit® RS100 (3:1, w/w ratio)].

tablets containing disintegrant than in those without disintegrant. Depending on the coating layer structures, the release profiles varied widely. The tablet containing disintegrant that was coated with a single layer of Eudragit® S100 showed colonic release after the lag time. However, this colonic-release profile was significantly hindered by a secondary coating of Eudragit® RS100. When a tablet containing disintegrant was coated with a binary blend of Eudragit® S100 and Eudragit® RS100 (3:1, w/w ratio), the zero-order sustained release pattern was obtained. Eudragit® RS100 is a pH-independent polymer that is used to control release rate in aqueous media. The disintegration force of Primojel® was not enough to easily break the coating membrane of Eudragit® RS100. Interestingly, the tablet coated with a mixture of pH-dependent Eudragit® S100 and pH-independent Eudragit® RS100 began drug release without any lag time when the gastric fluid was replaced by intestinal fluid.

Based on these findings, the colonic-release tablet containing inclusion complex and disintegrant could be useful for drug delivery to the proximal small intestine and upper colon. The current colonic-release tablet may also be useful for targeted delivery of various non-steroidal anti-inflammatory drugs and high molecular-weight peptides with low stability in the stomach.

3.2. Evaluation of rat intestinal toxicity

Histological observations of intestinal toxicity in rats after direct administration of naproxen suspension and inclusion complex into the intestine are shown in Fig. 7. The duodenal mucosal tissues showed focal disrupted surface mucosa (arrow) with mild mononuclear inflammatory cell infiltration in the lamina propria of rats treated with naproxen suspension. In the naproxen inclusion complex-treated rats, the mucosal mem-

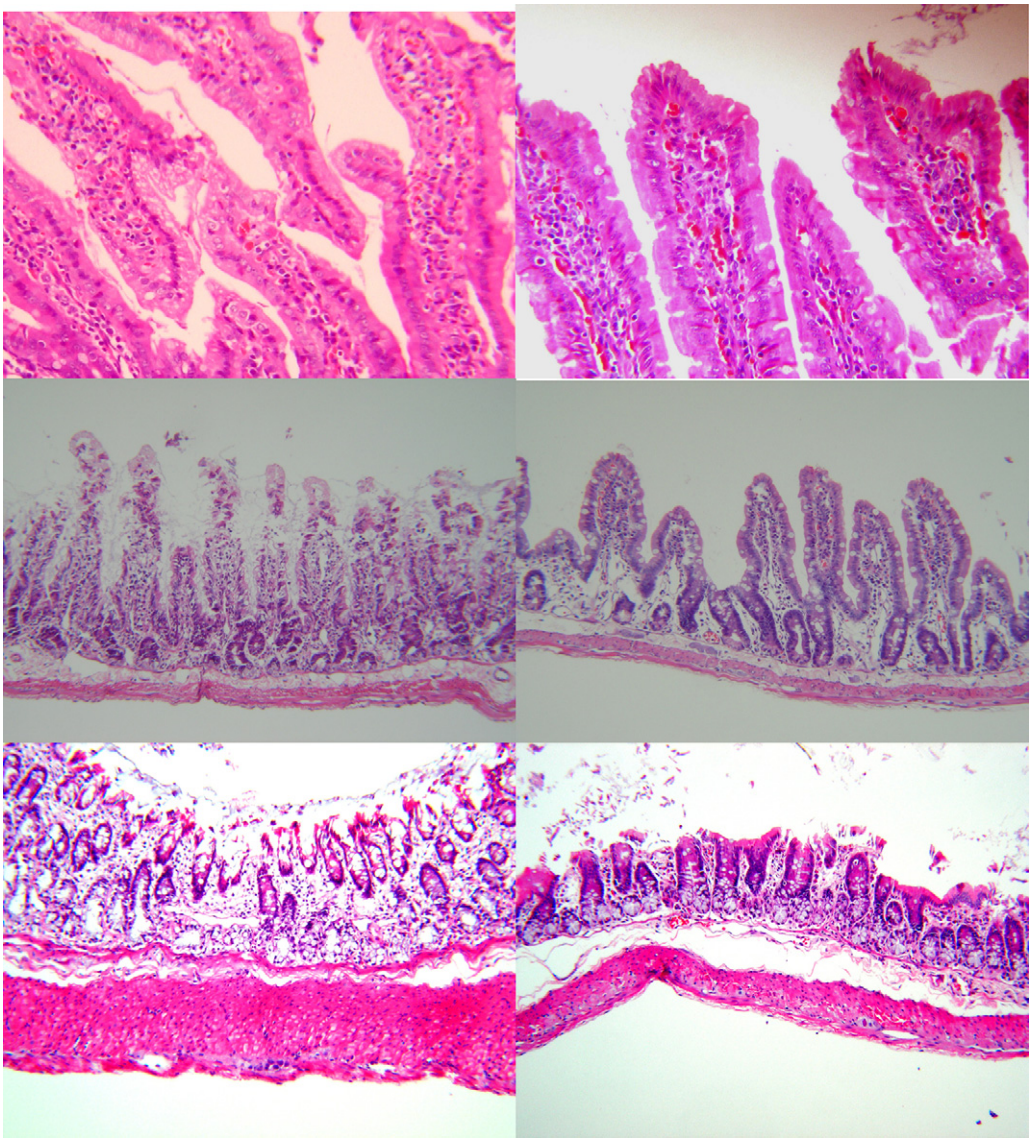

Fig. 7. Histological examination of rat intestinal segments after direct administration of naproxen and inclusion complex. Left: naproxen-treated; right: naproxen inclusion complex-treated; top: duodenum; middle: ileum; bottom: colon.

brane of the villi was relatively intact, and the inflammatory cell infiltration was not remarkable. The ileal mucosa also showed superficial erosion and necrosis with slight inflammatory cell infiltration in naproxen-treated rats. The naproxen inclusion complex-treated rats exhibited slightly shortened and irregular ileal mucosa, but no superficial erosion or necrosis, and the inflammatory cell infiltration was unremarkable. The colonic mucosa in naproxen-treated rats showed diffused superficial erosion and slight inflammatory cell infiltration, while inclusion complex-treated colonic mucosa had mild focal erosion without remarkable inflammatory cell infiltration. Although toxicological examinations of naproxen inclusion complex with 2-HPßCD were not carried out in human subjects, this preliminary *in vivo* histological evaluation of rat intestinal tissues suggested that the gastrointestinal side effects of the naproxen could be minimized by the inclusion complexation. Recently, effect of naproxen on upper gastrointestinal tract mucosal injury in healthy subjects was reported by endoscopic study (Wilder-Smith et al., 2006). The *in vivo* characterization of this colonic-release delivery system in human volunteers is also of our continuous concern.

4. Conclusions

A colonic-release tablet was obtained when a core tablet containing inclusion complex and disintegrant was coated with a single-layer of Eudragit® S100 after a predetermined 4–6 h lag time, depending on the type of disintegrant, plasticizers and structures of coated layers. Moreover, the inclusion complex provided potential advantages by reducing undesirable gastrointestinal damages of naproxen. The current colonic-release tablet could be useful to deliver drugs like naproxen in a high magnitude to the proximal intestine and upper colon to treat intestinal diseases like colitis and Crohn's disease, with reduced intestinal damages.

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