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Research paper

# Use of spray-dried chitosan acetate and ethylcellulose as compression coats for colonic drug delivery: Effect of swelling on triggering *in vitro* drug release

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ABSTRACT

Spray-dried chitosan acetate (CSA) and ethylcellulose (EC) were used as new compression coats for 5-aminosalicylic acid tablets. Constrained axial or radial swelling of pure CSA and EC/CSA tablets in 0.1 N HCl (stage I), Tris–HCl, pH 6.8 (stage II), and acetate buffer, pH 5.0 (stage III), was investigated. Factors affecting *in vitro* drug release, i.e., % weight ratios of coating polymers, dip speeds of dissolution apparatus or pH of medium or colonic enzyme (β-glucosidase) in stage III, and use of a super disintegrant in core tablets, were evaluated. Swollen CSA gel dissolved at lower pH and became less soluble at higher pH. The mechanism of swelling was Fickian diffusion fitting well into both Higuchi's and Korsmeyer–Peppas models. EC:CSA, at 87.5:12.5% weight ratio, provided lag time rendering the tablets to reach stage III (simulated colonic fluid of patients), and the drug was released over 90% within 12 h. The system was a dual time- and pH-control due to the insolubility of EC suppressing water diffusion and the swelling of CSA in the stages I and II. The erosion of CSA gel in the stage III induced the disintegration of the coat resulting in rapid drug release. The lower dip speed and higher pH medium delayed the drug release, while a super disintegrant in the cores enhanced the drug release and no enzyme effect was observed.



## 1. Introduction

Over the last decade, many colonic drug delivery systems have been developed in the treatment of inflammatory bowel disease (IBD) to improve drug efficacy especially for local action and to prevent side effects of drugs [1–4]. Several oral dosage forms, which possess an appropriate lag time for colonic drug delivery, have been designed. Among them, compression-coated tablets using biodegradable polymers as coating materials such as pectin/hydroxypropyl methylcellulose (HPMC) or pectin/chitosan or guar gum (GG)/xanthan gum (XG) or GG alone are reliable alternative choices [5–12], while the matrix and multilayer tablets failed to target the colon [5]. Gamma-scintigraphy of 5-fluorouracil tablets compression-coated with GG and XG showed that the tablets were disintegrated between 4 and 6 h after oral administration in all human volunteers with a further spread of tracer into the ascending, transverse, descending and sigmoidal colon [9].

Recently, chitosan and its salts have been widely used as carriers in controlled release drug delivery systems such as film and gel formers, matrix granules, beads, and microspheres [3,4,13–16]. Spray-dried chitosan salts as glutamate, aspartate, lactate and hydrochloride were prepared and applied for colonic drug delivery according to the degradability by colonic enzymes [17]. In our previous study, spray-dried chitosan acetate (CSA) was used in combination with HPMC as compression-coating materials for 5-aminosalicylic acid tablets [18]. The system provided a new concept based on a combination of time-, pH-, and enzyme-controlled colon specific drug delivery. *In vitro* drug release was studied in 0.1 N HCl to simulate gastric condition for 2 h (stage I), then in Tris–HCl, pH 6.8, to simulate intestinal fluid for 3 h (stage II), and in acetate buffer, pH 5.0, to simulate colonic fluid of IBD patients until 24 h (stage III). The appropriated lag time was controlled by the swelling of CSA and HPMC in 0.1 N HCl and the less solubility of CSA in, pH 6.8, Tris–HCl. The drug release in the colonic acid fluid was due to the dissolution at low pH and the degradation by colonic enzymes of CSA. Ethylcellulose (EC), a hydrophobic polymer, has been used as coating materials to suppress drug release in many sustained release dosage forms [19–22]. In the present study, EC was used to replace HPMC, in combination with CSA, as novel coatings for colonic delivery of 5-aminosalicylic acid (5-

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ASA). Swelling behaviors of CSA and EC/CSA in different media were investigated. Factors affecting the drug release, i.e. % weight ratios of coating polymers, dip speeds of dissolution apparatus or pH of medium or colonic enzyme (β-glucosidase) in stage III and use of a super disintegrant in core tablets, were examined.

## 2. Materials and methods

### 2.1. Materials

The materials used in this experiment, and the suppliers are as follows: 5-aminosalicylic acid (lot & filling code 400895/1 13799, Fluka, Switzerland); β-glucosidase (lot & filling code 1264252 34706394, Fluka, Switzerland); chitosan, molecular weight ($M_W$) of 45 kDa, 87% degree of deacetylation (COA 280604, Sea Fresh Co. Ltd., Thailand); α-lactose monohydrate (Tablettose 80®, Lot No. 9928, Meggle, Germany); and sodium starch glycolate (Explotab®, Batch No. E9963, Rama Production, Thailand). Ethylcellulose (10 cp, Std. Prem. FP, Batch No. RB24013T10) was a gift from Colorcon Asia Pacific Pte. Ltd., Singapore. Other chemicals were of reagent grade.

### 2.2. Preparation of CSA

Chitosan flakes ($M_W$ 45 kDa, 87% DD) were dissolved in an aqueous acetic acid to make a 3.5% w/w solution. The solution was sprayed at an inlet temperature of 125 + 2 °C using a spray dryer (Minispray Dryer, Büchi 190, Switzerland). The obtained powders were spherical agglomerate particles with mean diameter of about 14 μm [18].

### 2.3. Swelling behaviors of CSA and EC/CSA tablets

Real-time swelling and erosion behaviors of pure HPMC or drug–polymer matrix tablets were carried out by observation of the tablets immersed in the distilled water or dissolution media [23–25]. This method provides an advantage over gravimetric methods because all the data are obtained "*in situ*", and there were no interferences during weighing and error from removing excess solvent from the samples. Pure CSA, each weighing 300 mg, was compressed into tablets (about 10 mm in diameter) at a fixed compression force of 10 kN using a hydraulic press (Specac, Inc., USA). Radial expansion of each tablet in different media, i.e. 0.1 N HCl, Tris–HCl, pH 6.8, and acetate buffer, pH 5.0, at ambient temperature (30 + 2 °C) was measured. The tablet was clamped between two glass slides so that water uptake was allowed only through the side of the tablet (Fig. 1a and b) [23]. We also modified open-ended tubes with the same diameter of the tablets and used them to observe the axial expansion of the tablets. The swelling or rubbery region of each tablet was measured at least 3 points (Fig. 1c and d). The experiment was done in triplicate and % swelling was calculated by the following equations:

$$\%\ \text{Swelling}_{\text{axial}} = \frac{(h_t - h_o)}{h_o} \times 100 \quad (1)$$

$$\%\ \text{Swelling}_{\text{radial}} = \frac{(A_t - A_o)}{A_o} \times 100 \quad (2)$$

where $h_o$ and $A_o$ are thickness and upper surface area ($\pi[d_o/2]^2$, $d_o$, diameter) of the original dry tablet, respectively, while $h_t$ and $A_t$ are measured from axial and radial swelling at time $t$, respectively. Furthermore, the radial swelling of CSA tablets without any constraints was also observed in all media as well as that of tablets compressed from blends of EC:CSA at 87.5:12.5% weight ratio and pure EC.

Swelling kinetics of CSA tablets in each medium was analyzed by the application of the following equations [26,27]:

Korsmeyer–Peppas model;

$$S = k_s \cdot t^n \quad (3)$$

Higuchi's model;

$$S = k_s' \cdot t^{1/2} \quad (4)$$

First order kinetics;

$$\log S = k_s'' \cdot t \quad (5)$$

where S, $t$ and $k_s$, $k_s'$, $k_s''$ are % swelling (axial or radial), time (hours), and swelling kinetic constant of each model, respectively.

### 2.4. Preparation of 5-ASA compression-coated tablets

Core A containing 5-ASA and α-lactose monohydrate was compress-coated with dry blends of EC:CSA at various % weight ratios at a compression force of 10 kN using a hydraulic press (Table 1). Core B containing 5-ASA, α-lactose monohydrate and a super disintegrant, sodium starch glycolate, compress-coated with EC:CSA at 87.5:12.5% weight ratio was also prepared.

### 2.5. In vitro drug release study

*In vitro* release of 5-ASA from compression-coated tablets was studied using a USP dissolution apparatus 3 (BIO-DIS®, RRT8, Caleva Ltd., UK). The drug dissolution was determined in 0.1 N HCl for 2 h (stage I, simulated gastric fluid), later in Tris–HCl buffer, pH 6.8, for 3 h (stage II, simulated intestinal fluid) and then in acetate buffer, pH 5.0, until 24 h (stage III, simulated colonic fluid of patients with IBD [1]). The amount of drug was analyzed by UV spectrophotometry (Lambda 2, Perkin-Elmer, USA) at $\lambda_{max}$ of 301.5 nm in 0.1 N HCl, 334.5 nm in Tris–HCl, pH 6.8, and 299 nm in acetate buffer, pH 5.0. Factors affecting dissolution profiles of

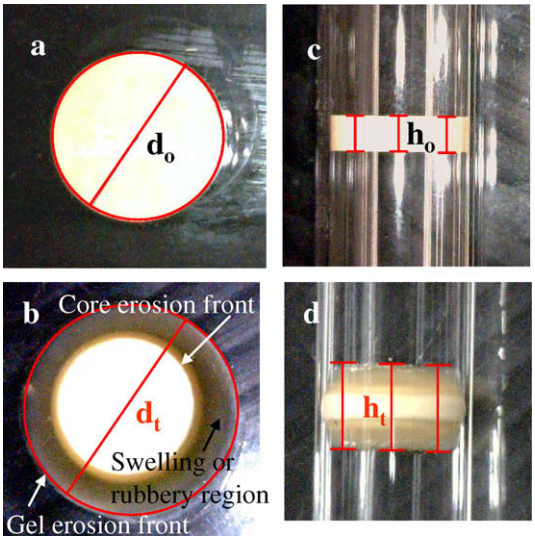


**Fig. 1.** Swelling study of CSA tablets along (a) axial and (b) radial directions.

**Table 1**
Formulations of different core tablets

| Components | Core A (mg) | Core B (mg) |
|---|---|---|
| 5-Aminosalicylic acid | 50 | 50 |
| Sodium starch glycolate | – | 25 |
| α-Lactose monohydrate | 50 | 25 |
| Total core weight | 100 | 100 |
| EC:CSA (100:0,95:5,90:10, 87.5:12.5,87:13,86:14) | 200 | 200 |
| Total tablet weight | 300 | 300 |

5-ASA were studied from various conditions, i.e. core A compress-coated with CSA:EC at various % weight ratios, core A compress-coated with CSA:EC at 87.5:12.5% weight ratio using dip speeds of the reciprocate cylinders of 5 and 20 dips per minute (dpm) or different pH media (5.0 and 7.0) or adding colonic enzyme (β-glucosidase) in stage III as well as core B compress-coated with CSA:EC at 87.5:12.5% weight ratio.

## 3. Results and discussion

### 3.1. Swelling behaviors of CSA and EC/CSA tablets in different media

Frequently, swelling and erosion of pure polymer or drug–polymer matrices in the dissolution medium have been reported, since they played an important role in controlling the drug release from the hydrophilic matrices [23–25,28,29]. Swelling behaviors of pure CSA tablets in different media, i.e. 0.1 N HCl, Tris–HCl, pH 6.8, and acetate buffer, pH 5.0, are well illustrated in Figs. 2 and 3. After exposure to the media, the penetration of water into the tablets resulted in subsequent hydration/swelling and gel formation at the interface of the tablets and the medium. The gel erosion front was moving outward resulting in the expansion of swelling or rubbery region, while the boundary of the glassy core or the core erosion front (Colombo et al. defined as "swelling front") was moving inward [23,25]. The outer rubbery region became loose according to the increased time. Fig. 4 shows that the expansion of axial swelling is faster and higher than the swelling along radial direction. This is in agreement with the studies by Strübing et al. and

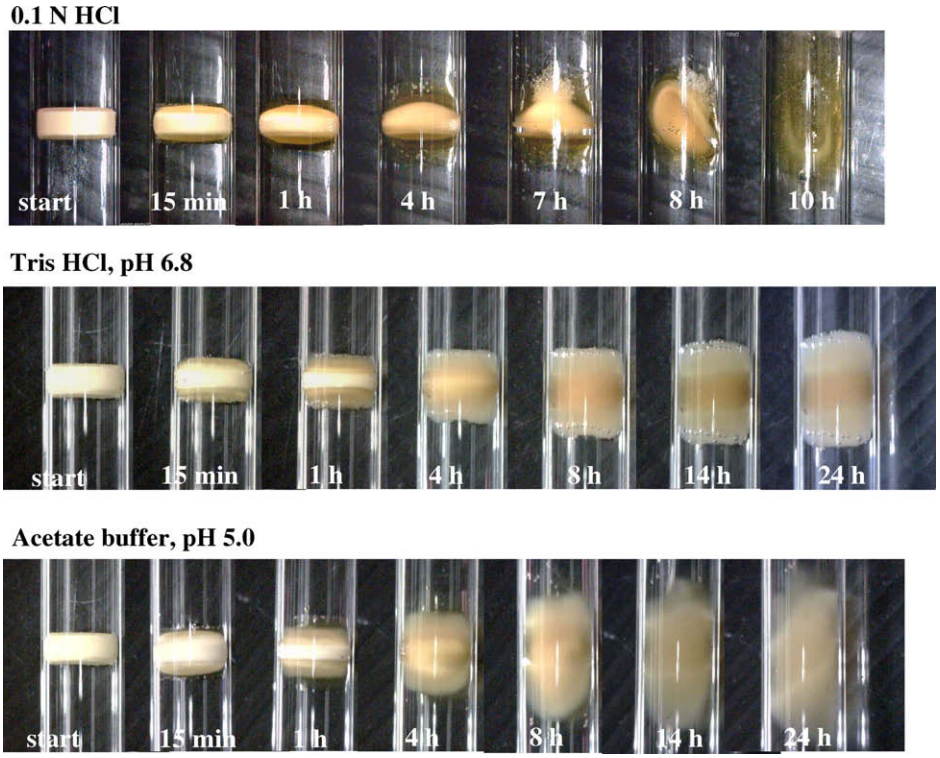


**Fig. 2.** Axial swelling of CSA tablets in various media.

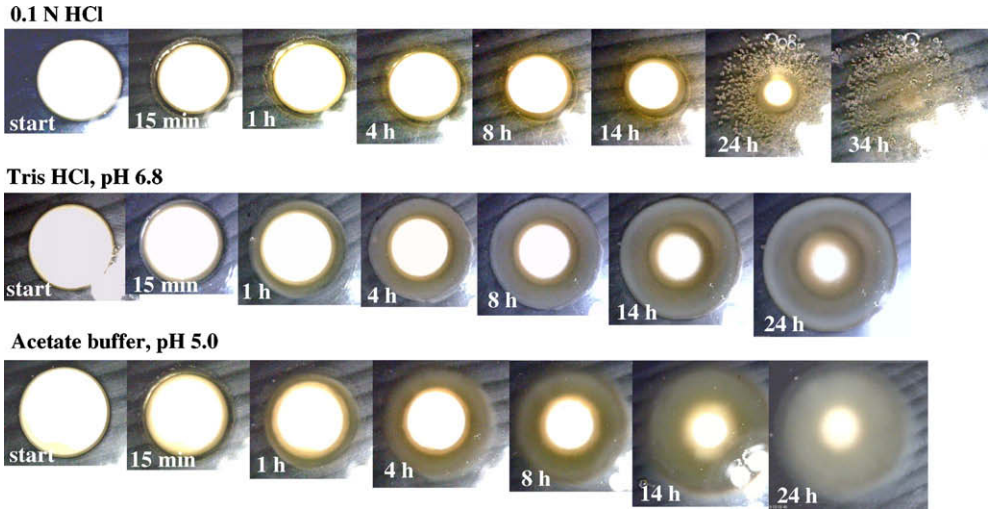


**Fig. 3.** Radial swelling of CSA tablets in various media.

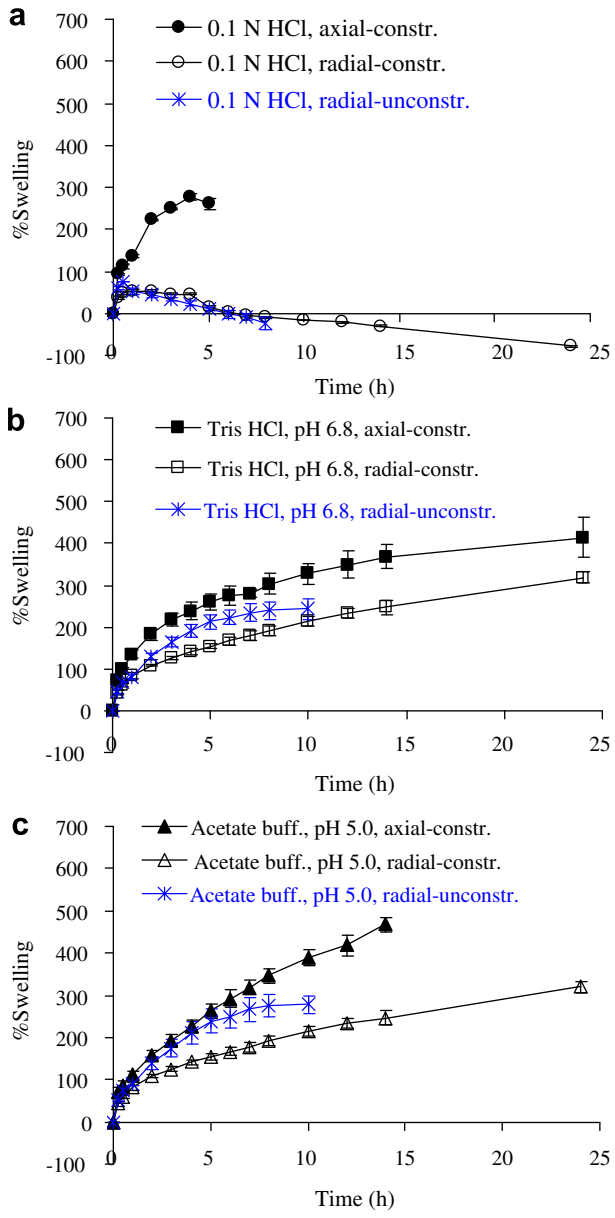


**Fig. 4.** % Swelling of CSA tablets in (a) 0.1 N HCl, (b) Tris–HCl, pH 6.8, and (c) acetate buffer, pH 5.0 ($n = 3$).

Sriamornsak and Kennedy [28,30]. The latter suggested that preferential axial expansion may be due to the release of stresses along axial direction developed during powder compaction [30]. The larger exposure area of the radial surfaces also enhanced the swelling process, since the value of $(2\pi[d_o/2]^2)$ is higher than that of $(2\pi[d_o/2]h_o)$. In 0.1 N HCl, CSA tablets formed a clear yellow gel which was completely dissolved within 10 and 34 h along axial and radial direction, respectively. The measured axial expansion was about 276% at the 4th hour before the interference from gas bubbles occurred (Fig. 4a). The production of gases was due to the high porosity of CSA powders (about 73%, data from our previous study [18]). The radial swelling readily decreased due to the dominance of rapid gel erosion in subsequent with dissolution in the acid medium. In Tris–HCl, pH 6.8, CSA tablets formed insoluble white turbid gel, and the swelling along axial and radial directions at the 24th hour was about 413% and 319%, respectively (Fig. 4b). The % swelling in acetate buffer, pH 5.0, was the highest and the axial expansion at the 14th hour was about 467% prior to complete core erosion, while the radial swelling was about 319% at 24th hour (Fig. 4c). According to the $pK_a$ value of about 6.2–7.0, chitosan will be protonated at low pH and the ionization degree of amine groups becomes less at higher pH, and hence less soluble gel will be formed [31,32]. The unconstrained radial swelling of the tablets in all media was faster and higher than the constrained ones and the glassy core completely eroded within 10 h in Tris–HCl and acetate buffer, while in 0.1 N HCl, all the cores completely dissolved within 8 h.

**Table 2**
Swelling kinetics of CSA tablets in various media

| Media | $S = k_s t^n$ | $S = k_s' t^{1/2}$ | $\text{Log}S = k_s'' t$ |
|---|---|---|---|
| | $n$ ($r^2$) | $k_s'$ ($r^2$) | $k_s''$ ($r^2$) |
| 0.1 N HCl, axial | 0.41 (0.9379) | 1.29 (0.9801) | 0.13 (0.9098) |
| 0.1 N HCl, radial* | – | – | – |
| Tris–HCl, pH 6.8, axial | 0.43 (0.9987) | 0.80 (0.9658) | 0.03 (0.6176) |
| Tris–HCl, pH 6.8, radial | 0.42 (0.9978) | 0.62 (0.9988) | 0.03 (0.7103) |
| Acetate buffer, pH 5.0, axial | 0.45 (0.9841) | 1.24 (0.9947) | 0.06 (0.8443) |
| Acetate buffer, pH 5.0, radial | 0.41 (0.9804) | 0.77 (0.9126) | 0.04 (0.8713) |

* Swelling decreased due to gel erosion.

Water uptake or hydration results in swelling of polymers which is the main factor in controlling the drug release from the swelling system. To determine the mechanism and rate of water uptake, kinetics of swelling of CSA tablets is analyzed by the application of Korsmeyer–Peppas model, Higuchi's model and first order kinetics as shown in Table 2. Swelling kinetics of CSA tablets in Tris–HCl and acetate buffer (axial) are Fickian diffusion, since they fitted well with both Higuchi's ($r^2$ in range of 0.9658–0.9947) and Korsmeyer–Peppas models ($r^2$ in range of 0.9841–0.9987 with $n$ value close to 0.45 of a cylindrical shape) [33]. Our results are in good agreement with the study of Bajpai et al. [34], who suggested that a Fickian diffusion is characterized by a solvent diffusion rate slower than the polymer relaxation rate, which was due to the fact that the polymer will be in the rubbery state and polymer chains will have a higher mobility that allows an easier penetration of the solvent. Dahlberg et al. [35] reported that the swelling behavior of HPMC matrix incorporating the hydrophilic drug, antipyrine, followed a linear function of $t^{1/2}$ which was diffusion controlled. The axial swelling of CSA tablets, except for that in 0.1 N HCl, was more diffusion controlled ($n = 0.45$ and 0.43) than the radial swelling ($n = 0.42$ and 0.41), which could be explained by the preferential expansion as mentioned above. Swelling kinetics of CSA tablets in all media did not follow the first order kinetics.

In Fig. 5, erosion of the tablets induced by swelling and dissolution of CSA gel in acid media is observed from EC:CSA (87.5:12.5% weight ratio) tablets, while no effect is observed in Tris–HCl as well as those of pure EC tablets.

### 3.2. In vitro drug release study

#### 3.2.1. Effect of weight ratio of coating polymers

Fig. 6 shows the release of 5-ASA from the tablets (core A) coated with blends of EC:CSA in various % weight ratios. The polymer blends, especially at the ratios of 87:13 and 87.5:12.5 provided a proper lag time of about 3–6 h, and the system was considered to be sufficient for colonic arrival [36]. The delayed release of 5-ASA in 0.1 N HCl and Tris–HCl, pH 6.8 (stages I and II), was time-controlled mechanism, which was mainly due to the insolubility of EC preventing the penetration of water into the core tablets. Although the swollen dissolving gel of CSA in 0.1 N HCl could induce the erosion of the outer coat comprising EC and CSA, it did not affect the drug release in the first 2 h. Even pure CSA alone could swell and form less soluble gel in Tris–HCl, pH 6.8, the use of CSA in combination with EC showed no swelling effect in this

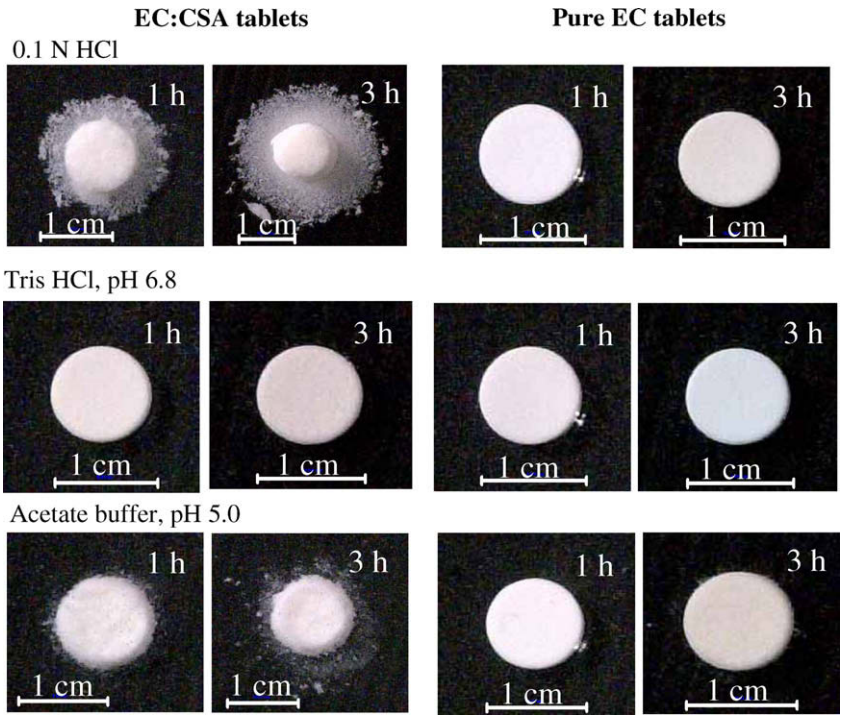


**Fig. 5.** Unconstrained swelling of EC:CSA at 87.5:12.5% weight ratio in various media ($n = 3$).

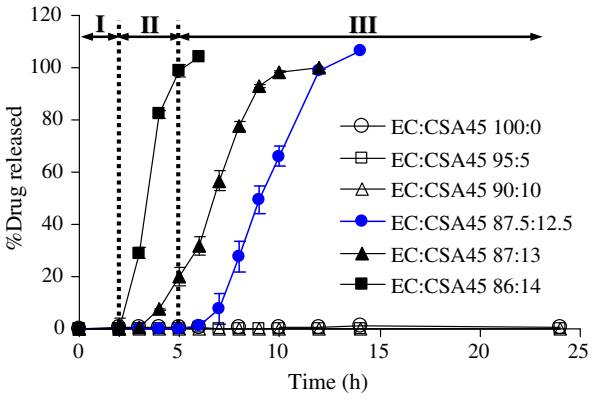


**Fig. 6.** Dissolution profiles of 5-ASA from tablets (core A) compress-coated with EC:CSA at various % weight ratios during stages I–III ($n = 3$).

medium, and hence the drug release was delayed. After arrival at stage III (acetate buffer, pH 5.0, for colonic pH in IBD patients, dip speed of 5 dpm), the drug release was over 90% within 12 h. The increased rate of drug release in this stage was attributed to the swelling with subsequent erosion of CSA gel in the colonic acid medium inducing disintegration of the polymer coating. The use of EC in the replacement of HPMC as compression coatings for 5-ASA tablets consumed smaller amount of CSA to provide the same drug release pattern even in the condition of lower dip speed [18].

### *3.2.2. Effect of dip speed, pH of medium, disintegrant in the core tablets and colonic enzyme*

Wong et al. [37] reported that the dip speeds of the reciprocating cylinder of the dissolution apparatus in stage III >5 cycles/min (dpm) may be unrealistic because transit and other movements of colon are relatively slow compared to those of the small intestine. In this study, the dip speed was decreased from 20 dpm to 5 dpm

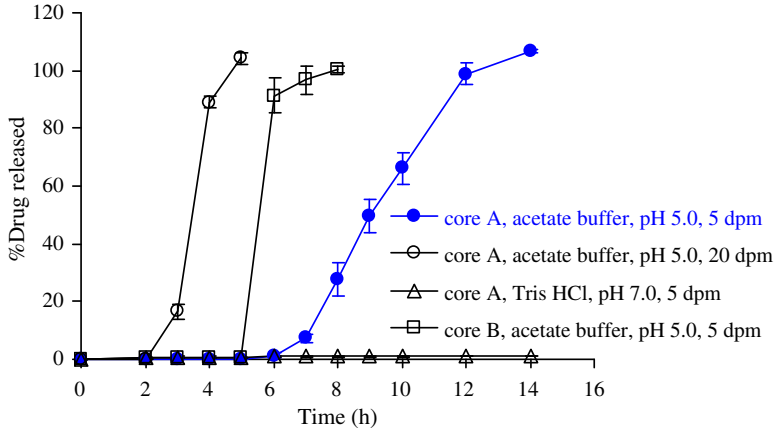


**Fig. 7.** Dissolution profiles of 5-ASA compress-coated tablets (cores A and B) in various conditions during stages I–III ($n = 3$).

resulting in the decrease of 5-ASA release from coated tablets (Fig. 7).

The slower drug release with longer period of lag time was observed in the simulated colonic fluid of healthy volunteers (Tris–HCl buffer, pH 7.0) compared to that in the simulated colonic fluid of IBD patients (acetate buffer, pH 5.0) (Fig. 7). The pH effect on drug release was in an agreement with the result of the tablets compress-coated with HPMC:CSA in our previous study [18].

The release of 5-ASA from the core tablet, containing a super disintegrant, sodium starch glycolate (core B), compress-coated with blends of EC:CSA at 87.5:12.5% weight ratio provided rapid drug release over 90% within 6 h (Fig. 7). Swelling of the super disintegrant resulted in the bursting of the core tablets, and helped the rate of drug release increase. In our previous study, the expansion of the disintegrant also enhanced the drug release from the tablets compression-coated with HPMC and CSA [18].

The effect of β-glucosidase enzyme added in the stage III to mimic the colonic fluid was also studied, and no effect on the drug release was observed from core A compress-coated with blends of EC:CSA at 87.5:12.5% weight ratio (data not shown). The disintegration of the EC/CSA coat due to the swelling with subsequent erosion of CSA gel in the acid medium induced the rapid drug release rather than the degradation of CSA by the enzyme. In our previous study, the degradation of CSA tablets by colonic enzyme adding in the medium was only 10% higher than that with no enzyme [18].

## 4. Conclusion

The use of EC in combination with CSA shows the potential as new compression coats for colonic drug delivery. These coatings are able to suppress the release of 5-ASA until it reaches the colon. The drug release is based on time- and pH-controlled system due to the water insolubility of EC and the gel formation of CSA the solubility of which depends on pH of the media. Drug permeation and *in vivo* test are suggested for further study in the development of this colonic drug delivery system.

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