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*Research Article*

# Comparison Between the Effect of Strongly and Weakly Cationic Exchange Resins on Matrix Physical Properties and the Controlled Release of Diphenhydramine Hydrochloride from Matrices

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***Abstract.*** This study focused on investigating and comparing between the effect of the strongly cationic exchange resin, Dowex 88 (Dow88), and the weakly cationic exchange resin, Amberlite IRP64 (Am64), on the physical properties of matrices and their drug release profiles. The matrices were prepared by direct compression of Methocel K4M (HPMC) or Ethocel 7FP (EC) polymeric matrix formers and contained diphenhydramine hydrochloride as a model drug. The addition of Dow88 to the matrices decreased matrix hardness and increased thickness, diameter, and friability. In contrast, the addition of Am64 increased matrix hardness and maintained the original thickness, diameter, and friability. In deionized water, both resins lowered drug release from HPMC-based matrices by virtue of the gelation property of matrix former and the drug exchange property of embedded resin, in other words *in situ* resinate formation. Dow88 strongly dissociated and lowered the drug release to a greater extent than Am64, which was weakly dissociated. However, Am64 could retard drug release under simulated gastrointestinal conditions. EC-based matrices containing either resin displayed a propensity for disintegration caused by swelling and wicking (water adsorption) actions by the resin. The results of this study provided useful information on the utilization of ion exchange resins as release modifiers in matrix systems.

**KEY WORDS:** controlled release; matrices; physical properties; strongly cationic exchange resin; weakly cationic exchange resin.

## INTRODUCTION

Ion exchange resins are insoluble, crosslinked copolymers that can reversibly bind dissociated drugs via ion exchange. Resins have diversified applications in chemical and pharmaceutical industries. In pharmaceutics, they are often used as drug carriers and to control the rate of drug release. Controlled release systems using resin technology can be administered in a variety of forms including tablet, capsule, powder, gum, and liquid suspension. The bitter and unpleasant taste of drugs is reduced when bound to resins; thus, patients are more compliant in consuming these "resinates." Furthermore, resins can be exploited as a disintegrant in tablet formulations (1–3).

Matrix systems, especially those prepared by direction compression, are a popular method for controlling the release of drugs (4). Materials used for forming matrices include hydrophobic or hydrophilic polymers. Drug release from matrices using hydrophobic polymers such as ethyl cellulose proceeds via diffusion through an almost intact matrix (5,6). Matrices made of hydrophilic polymers such as hydroxypropyl methylcellulose swell and form gels that may simultaneously erode if the molecular weight of the polymer is low. Nonetheless, the release of water-soluble drugs is governed primarily by diffusion rather than erosion of gelled matrices (7,8). Common methods of modifying drug release from matrices include selecting a suitable polymer, adjusting the polymer/drug ratio, admixing several polymers, and adding an excipient such as a pore former (4–9).

Recent studies have shown that resins can modify the release of drugs from matrices without the need for prior formation of a resinate. Thus, drug release may be governed by "*in situ* resinate formation" (10,11). Adding an ion exchange resin to modify the drug release may alter the physical properties of matrices such as hardness and friability (11). The literature suggests that strongly cationic exchange resins such as Amberlite IRP69 and Dowex 50W can retard drug release from matrices and adversely affect matrix hardness and friability. However, the mechanism of drug release modification and the effect of weakly cationic exchange resins on the physical properties of matrices have not been established. This information is necessary for adopting ion exchange resins as a release modifier for matrix systems.

Thus, the objective of this study was to investigate the effect of the weakly cationic exchange resin, Amberlite IRP64 (Am64), on the physical properties of matrices and their drug

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release profiles. In addition, the effect of the strongly cationic exchange resin, Dowex 88 (Dow88), on the matrix properties and drug release was investigated and compared to those of Am64. The matrices were prepared from either Methocel K4M hydroxypropyl methylcellulose (HPMC) or Ethocel 7FP ethyl cellulose (EC), which represented hydrophilic and hydrophobic polymeric matrix formers, respectively. In this study, the antihistamine diphenhydramine hydrochloride was chosen as a model drug. Diphenhydramine hydrochloride has a short half-life of approximately 5–6 h and is administered orally several times daily (12,13). The drug could be prepared in a controlled release matrix to provide improved convenience and patient compliance. Moreover, this drug was used in our previous work; the use of diphenhydramine hydrochloride in the current study allowed for a direct comparison to prior results (11).

## MATERIALS AND METHODS

### Materials

Methocel K4M hydroxypropyl methylcellulose (viscosity of 3,000–5,600 cps as a 2% solution in water and methoxyl and hydroxypropyl contents of 19–24% and 7–12%, respectively) and Ethocel 7FP ethyl cellulose (viscosity of 6–8 cps as a 5% solution in 80% toluene and 20% alcohol and a ethoxyl content of 48.0–49.5%) were kindly donated from Colorcon Ltd., UK (Dow Chemical Co., USA). Magnesium stearate (BP grade) was a gift from Glaxo Wellcome Vidhyasom, Thailand. Dowex 88 (Dow Chemical Co., USA), Amberlite IRP64, Amberlite IRP69, and diphenhydramine hydrochloride (Sigma Chemical Co., USA) were purchased from various suppliers. Other chemicals employed in the investigation were analytical grade or higher. Deionized water was used entirely in this work.

### Methods

#### *Preparation of Matrices by Direct Compression*

Fixed weight matrices were composed of diphenhydramine hydrochloride, a resin (Dow88 or Am64), magnesium stearate, and a matrix former (HPMC or EC). The drug content and lubricant were fixed at 30% and 1% *w*/*w*, respectively. The amount of resin was varied from 0% to 40% *w*/*w*, and the remainder of each matrix was composed of (percent *w*/*w*) matrix former. All required components were gently blended in a mortar for 10 min. Then, a total of 100 mg of each mixture was accurately weighed and carefully placed into a hydraulic hand press machine (Specac P/N 15011/25011, UK). The matrices were compressed using stainless steel flat-circular punches (6.35 mm in diameter) with a constant force and dwelling time of 5 t for 5 s. The produced matrices were stored tightly in containers until use.

#### *Thickness, Diameter, Hardness, and Friability of Matrices*

The thickness and diameter of ten matrices were measured with a micrometer (Sylvac S229, Switzerland), and hardness was measured with a texture analyzer (Stable Micro Systems TA.XT plus, UK). To this end, matrices were pressed by a stainless steel flat-face (6 mm in diameter) cylindrical probe moving at a constant speed (1 mm/s). The hardness value was read directly from the instrument and was given as the force that caused a diametrical break in the matrices. Friability was tested on a Roche friabilator. Twenty matrices were weighed ($W_1$) and placed into the friabilator operating at 100 rev for 4 min. The matrices were then weighed ($W_2$) again, and the friability (percent) was calculated by the equation: $100 \times (W_1 - W_2)/W_1$ (14).

#### *Drug Release from Matrices*

(a) In deionized water

Drug release was investigated in triplicate using a USP dissolution testing apparatus I (Dissolutest Prolabo, France) and 900 ml of deionized water at 37±1°C (15). The release test was conducted under a constant rotation (50 rpm). At predetermined times, 5 ml of the medium was withdrawn through a filter, and an identical volume of fresh medium was added to the vessels to maintain a constant volume. The withdrawn medium was assayed by an ultraviolet spectrophotometer (UV, Perkin Elmer Lambda 2, Germany) at 218 nm.

(b) Under simulated gastrointestinal conditions

A simulated gastrointestinal release study was conducted following the USP dissolution test for delayed release (method A) using an identical apparatus (15). Drug release was determined in 750 ml of a 0.1-N hydrochloric acid solution (HCl) for 2 h. Thereafter, 250 ml of a 0.2-M tribasic sodium phosphate solution ($Na_3PO_4$) was added into the vessels, and drug release into the buffered solution (pH 6.8) was determined. The rotation rate and temperature were maintained at 50 rpm and 37±1°C, respectively. At predetermined times, 5 ml of medium was withdrawn through a filter, and an identical volume of fresh medium was added to the vessels to maintain a constant volume. The withdrawn medium was assayed by UV at 218 nm, and appropriate blanks were used as correction factors. Drug release was evaluated in triplicate.

#### *Disintegration Test*

Disintegration tests were conducted with a USP disintegration testing apparatus (Sotax DT3, Switzerland) (15). At the beginning of each test, six matrices were placed into a basket-rack assembly with disks and deionized water at 37± 1°C. The disintegration time, defined as the moment the matrix disintegrated and passed through the assembly screen, was recorded for each sample.

#### *Scanning Electron Microscopy (SEM)*

The surface morphology of produced matrices was determined with a scanning electron microscope (SEM; Jeol JSM 5400, Japan) under a fixed magnification. Prior to viewing, matrices were firmly held on the top of stubs and sputter coated with gold in a vacuum evaporator (SPI Module Carbon Coater, USA).

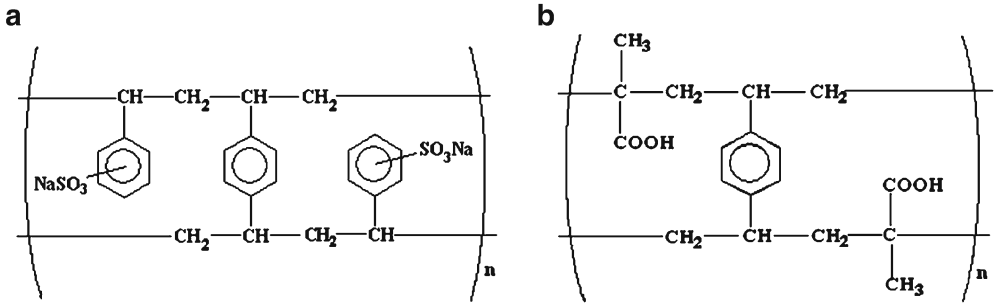


**Fig. 1.** Chemical structure of **a** Dow88 and **b** Am64, respectively

*Photograph of Matrices During Drug Release*

Photographs of matrices were taken under conditions identical to the release tests. At predetermined times, matrices were viewed with a digital camera in association with image analysis software (Dino-Lite Digital AM-313T Plus, Taiwan) under a fixed magnification.

*Swelling of Resin*

(a) Volume swelling

Equal weights of resin were placed into a 10-ml cylinder and were tapped until constant volume. The volume of resin

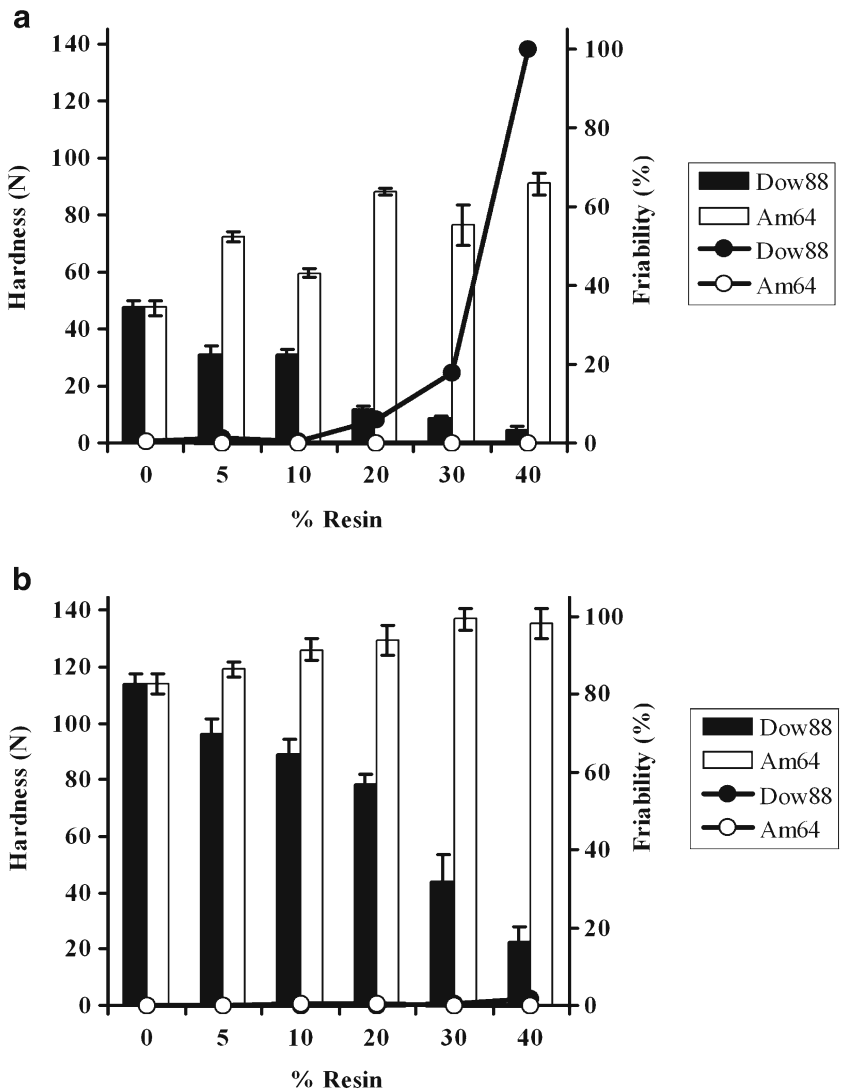


**Fig. 2.** Hardness (*bar graph*) and friability (*line graph*) of **a** HPMC- and **b** EC-based matrices containing various amounts of resin, respectively

($v_1$) was recorded, and an excess amount of water was carefully added into the cylinder. After 2 h, the volume of swollen resin ($v_2$) was recorded, and volume swelling (percent) was calculated according to the following equation: $100 \times (v_2 - v_1)/v_1$ (16).

(b) Weight swelling

Equal weights of resin ($w_1$) were placed in a centrifuge tube, and an excess amount of water was carefully added. After 2 h, the slurry was centrifuged at 2,000 rpm until the supernatant was clear. The supernatant was carefully removed with a micropipette, and the swollen resin was weighed ($w_2$). Weight swelling (percent) was calculated according to the following equation: $100 \times (w_2 - w_1)/w_1$ (17).

## RESULTS AND DICUSSION

### Dow88 and Am64

Dow88 is a strongly cationic exchange resin containing crosslinked styrene–divinylbenzene copolymer with sodium sulfonate groups as ion exchange sites (Fig. 1a) (18). This resin was milled in a mortar, and the fraction that passed through a 100-mesh sieve was used. Am64 is a weakly cationic exchange resin containing crosslinked methacrylic acid–divinylbenzene copolymer with carboxylic acid groups as ion exchange sites (Fig. 1b) (19). Am64 was obtained as a mixture of particles ranging in size from 100 to 400 mesh and therefore was used without modification. The results of an SEM study revealed that both resins were irregular in shape (figures not shown). The resins were insoluble in water but could hydrate and swell due to the dissociation of ion exchange sites.

### Physical Properties of Matrices

All matrices were prepared by direct compression. Matrices with or without resin had a fairly uniform weight (%CV ≤ 1) because mixture ingredients were weighed and directly fed into the compress (14). The hardness of HPMC- or EC-based matrices containing Dow88 continuously decreased with increasing amounts of embedded resin (Fig. 2), which was in agreement with SEM results. The density of matrix surface deteriorated (Fig. 3a *versus* b for HPMC-based matrices and Fig. 3d *versus* e for EC-based matrices, respectively) with increasing amounts of embedded resin. The deterioration in the hardness of HPMC-based

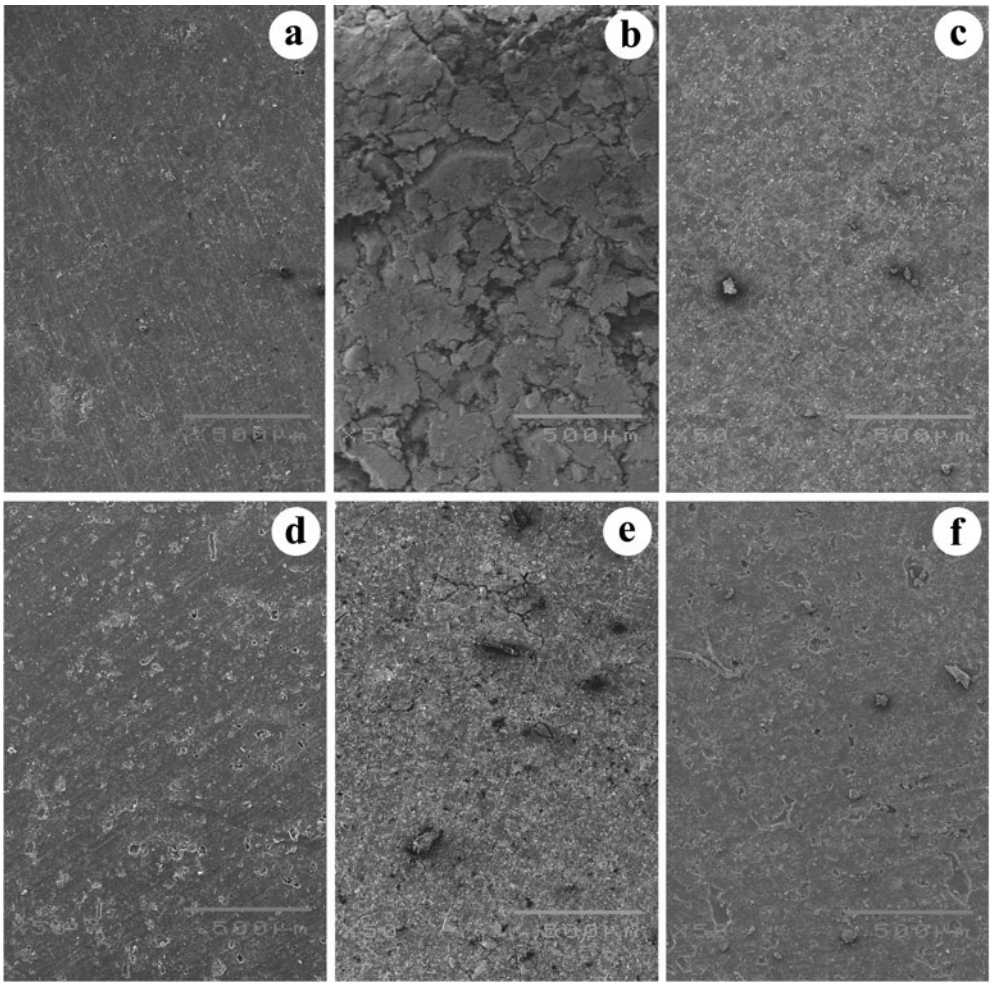


**Fig. 3.** Surface morphology of HPMC-based matrices containing **a** no resin, **b** 40% Dow88, and **c** 40% Am64 and EC-based matrices containing **d** no resin, **e** 40% Dow88, and **f** 40% Am64, respectively (×50 magnification)

matrices was higher than EC-based matrices because HPMC had lower compressibility than EC. This result was similar to those observed from the matrices containing Amberlite IRP69 (Am69) in the previous work (11). Am69 and Dow88 are crosslinked styrene–divinylbenzene copolymer resins with sodium sulfonate as ion exchange sites. Am69 is a gel-type (lowly crosslinked copolymer) resin, whereas Dow88 is a macroporous-type (highly crosslinked copolymer) resin (18–20). Thus, hardness results confirmed that crosslinked styrene–divinylbenzene copolymer resins had poor compressibility regardless of resin type or degree of crosslinking.

Interestingly, the hardness of HPMC- or EC-based matrices containing Am64 increased as the amount of embedded resin increased (Fig. 2). Coincidently, the matrices maintained smooth and compact surfaces (Fig. 3a *versus* c for HPMC-based matrices and Fig. 3d *versus* f for EC-based matrices, respectively). This result differed from those observed in matrices containing either Dow88 or Am69 (11), which implied that Am64 had higher compressibility than Dow88 and Am69. As already mentioned, Am64 is a crosslinked methacrylic acid–divnylbenzene copolymer resin, whereas Dow88 and Am69 are crosslinked styrene–divinylbenzene copolymer resins. It was possible that the copolymer chemistry governed the resin compressibility; the methacrylic acid–divinylbenzene copolymer resin might be inherently more compressible than styrene–divinylbenzene copolymer resins. Based on this virtue, Am64 was likely to be a superior release modifier for matrices because it did not undermine matrix hardness, which was observed with the addition of Dow88 and Am69.

Figure 2 also shows the friability of obtained matrices. The friability of HPMC-based matrices containing Dow88 increased markedly and could be divided into two phases (Fig. 2a). In the first phase, friability was gradually increased from 0.3% to 6.0% as the amount of Dow88 increased to 20%, corresponding to a decrease in hardness from 47.4 to 11.6 N. In the second phase, the friability of matrices containing 20% to 40% Dow88 increased dramatically from 6.0% to 100%, while the hardness slightly declined from 11.6 to 4.9 N. In contrast, the friability of EC-based matrices

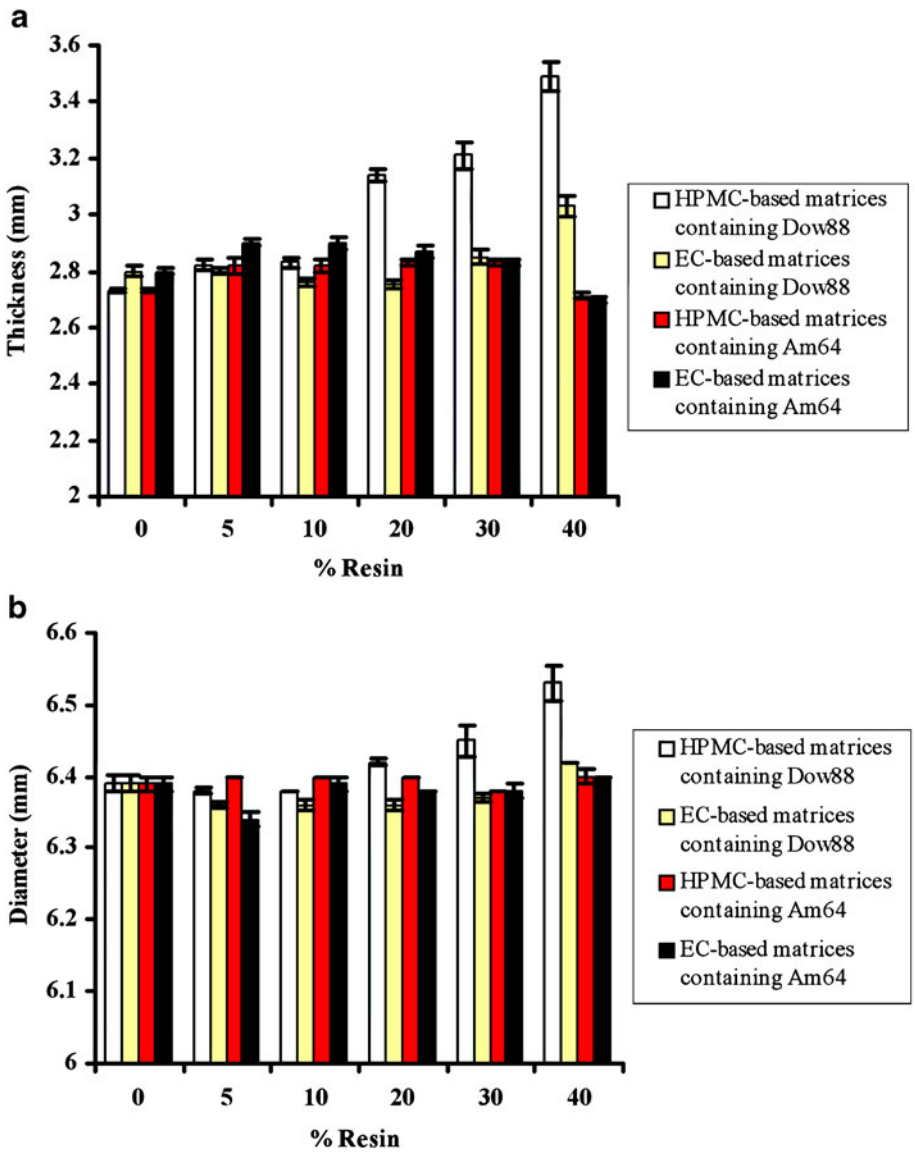


**Fig. 4.** Thickness **a** and diameter **b** of matrices containing various amounts of resin

containing Dow88 up to 40% increased slightly (<1.5%), although their hardness continuously decreased from 114.0 to 22.6 N (Fig. 2b). Indeed, this result concurred with those of previous studies and confirmed that a critical matrix strength was present in resin-embedded matrices (11). Below the critical matrix strength, friability would greatly increase with a decrease in hardness, otherwise remaining nearly unchanged. From Fig. 2, the critical matrix strength of HPMC-based matrices containing Dow88 was estimated to be approximately 12 N, which was similar to those of matrices containing Am69 (16–17 N). Therefore, HPMC-based matrices containing 20% to 40% Dow88 had a matrix hardness below 12 N, and the friability greatly increased with decreasing the matrix hardness. The friability of EC-based matrices containing Dow88 was nearly unchanged because their hardness had not declined below the critical matrix strength. In both HPMC- and EC-based matrices, the friability was maintained constant (≤0.3%) when Am64 was added to the matrices (Fig. 2). This result was due to the high compressibility of Am64, which increased the hardness of the obtained matrices.

The thickness and diameter of the matrices are depicted in Fig. 4. The matrices had similar dimensions; however, HPMC-based matrices containing Dow88 had an increased thickness and diameter, particularly when the amount of embedded resin exceeded 10%. This result might be due to the severe decrease in hardness and inter-particulate binding of the matrices, which was a result of the poor compressibility of the original matrix and embedded resin. As mentioned above, the compressibility of HPMC and Dow88 was lower than EC and Am64, respectively. Therefore, Dow88 greatly weakened inter-particulate binding of the HPMC matrix, leading to a less compact and more relaxed matrix. Due to the superior compressibility of EC, matrix hardness and inter-particulate binding of EC-based matrices containing Dow88 were not lowered as severely as those of HPMC-based matrices containing Dow88. Instead, the matrices were strong enough to withhold matrix relaxation after punch withdrawal. As with Am64, it strengthened matrix hardness and inter-particulate binding. As a result, the density of HPMC- or EC-based matrices containing Am64 was maintained, producing an unchanged thickness and diameter.

## Drug Release from Matrices in Deionized Water

Drug release from HPMC-based matrices containing Dow88 is shown in Fig. 5a. The results revealed that drug release was lowered by the incorporation of Dow88 into the matrix, which was similar to the results of previous studies (10,11). The decrease in drug release was due to the gelation property of HPMC and the drug exchange property of embedded resin. Thus, the observed decrease was caused by "*in situ* resinate formation"; upon contact with water, the matrices formed a gel (Fig. 6) of which the drug was able to diffuse out. However, a portion of the dissolved drug became bound to the embedded resin via ion exchange and formed a resinate or drug–resin complex, resulting in a decrease in drug release. This decrease in drug release was more dramatic with increasing amounts of embedded resin due to an increase in resinate formation.

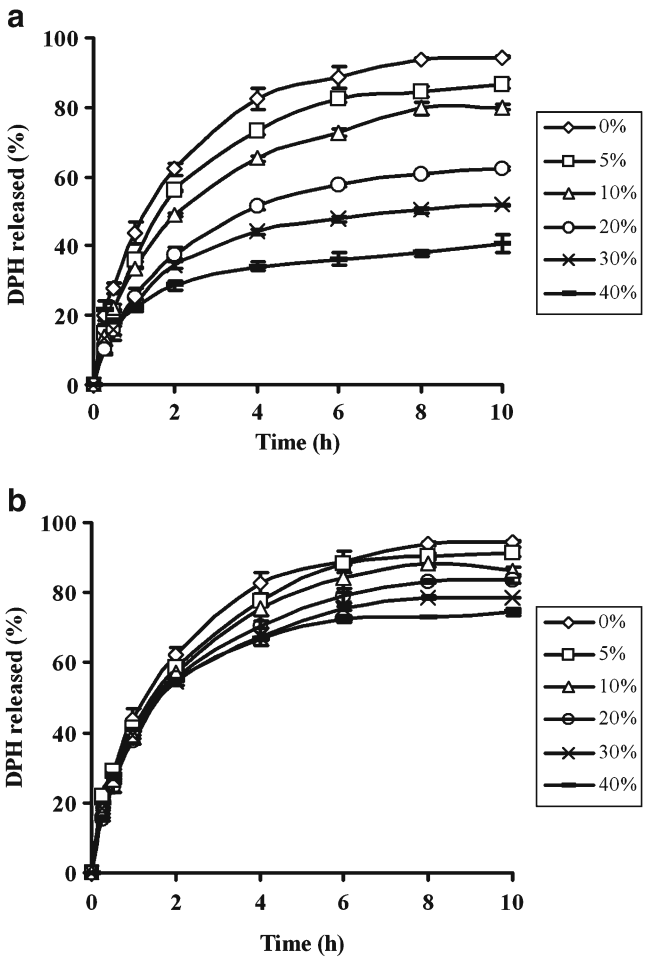


**Fig. 5.** DPH release from HPMC-based matrices containing various amounts of **a** Dow88 and **b** Am64, respectively

The incorporation of Am64 also decreased drug release from HPMC-based matrices (Fig. 5b) due to *in situ* resinate formation. Matrices containing Am64 formed a gel during drug release (Fig. 6); however, the decline in drug release from Am64 was clearly less than Dow88-embedded matrices due to the weaker drug exchange property of Am64 compared to Dow88. The ion exchange sites of Am64 and Dow88 are carboxylic and sulfonic groups, respectively, and the pH of drug solutions was between 5 and 6. Thus, the carboxylic group of Am64 ($pK_a$=4–6) weakly dissociated and provided lower drug exchange and *in situ* resinate formation than the sulfonic group of Dow88 ($pK_a$=1–2), which could strongly dissociate and interact with the dissolved drug (20,21).

It was observed that gelled matrices gradually eroded during drug release, and the erosion rate increased with increasing amounts of embedded resin due to a decrease in the amount of matrix former. For example, gelled matrices containing 40% Dow88 eroded so much that the small, collapsed residue could not be prepared for photographic viewing at the end of the release test (Fig. 6a). Nevertheless, matrices containing a higher amount of embedded resin provided a lower drug release in spite of higher matrix erosion. This phenomenon supported that drug release from the matrices was primarily governed by drug diffusion and

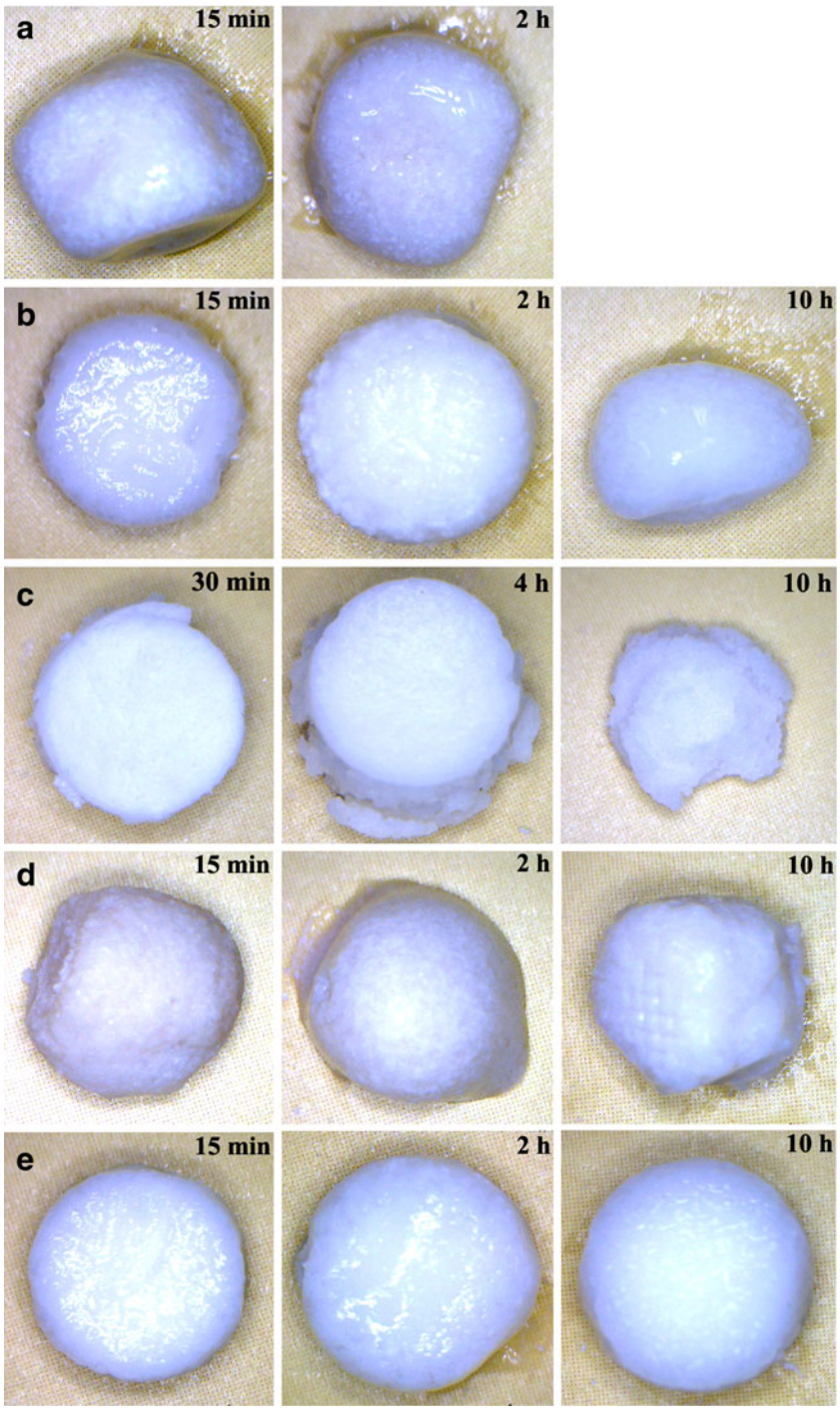


**Fig. 6.** Photographs during drug release of HPMC-based matrices containing **a** 40% Dow88 and **b** 40% Am64, EC-based matrices containing **c** 40% Am64 tested in deionized water, and HPMC-based matrices containing **d** 40% Dow88 and **e** 40% Am64 tested under simulated gastrointestinal conditions, respectively

exchange rather than matrix erosion (10,11). Moreover, it could be further evaluated by the kinetic analysis of release profiles. In general, the release data from gelled matrix systems can be analyzed according to the power law equation: $F_t=kt^n$, where $F_t$ is the fractional release of the drug (in the range of 0–70%) at time $t$, $k$ is the kinetic constant, and $n$ is the release exponent indicative of the release mechanism, respectively. According to the resultant kinetic parameters (Table I), all release profiles were satisfactorily fitted to the power law equation using appropriate $n$ values ($R^2 \geq 0.98$). The value of $n$ from the free-resin matrices was 0.569, indicating an anomalous transport corresponding to drug diffusion in the hydrated matrix and the polymer erosion (22,23). However, the matrices containing either resin exhibited a trend of decreasing $n$ values, *i.e.*, from 0.569 to 0.227 for Dow88 and from 0.569 to 0.410 for Am64,

**Table I.** Kinetic Parameters Analyzed from Release Profiles of HPMC-Based Matrices Containing Various Amounts of Dow88 or Am64

| | Dow88 | | | Am64 | | |
|---|---|---|---|---|---|---|
| % Resin | $n$ | $k$ ($h^{-n}$) | $R^2$ | $n$ | $k$ ($h^{-n}$) | $R^2$ |
| 0 | 0.569 | 0.421 | 0.999 | 0.569 | 0.421 | 0.999 |
| 5 | 0.547 | 0.386 | 0.999 | 0.504 | 0.412 | 0.999 |
| 10 | 0.465 | 0.355 | 0.994 | 0.539 | 0.392 | 1.000 |
| 20 | 0.422 | 0.260 | 0.977 | 0.492 | 0.372 | 0.991 |
| 30 | 0.349 | 0.251 | 0.980 | 0.434 | 0.383 | 0.993 |
| 40 | 0.227 | 0.239 | 0.977 | 0.410 | 0.395 | 0.991 |

respectively, elucidating that the release mechanism was not purely dependent on such drug diffusion, but coupled with drug exchange property from the embedded resin. The greater shift of $n$ values was observed from Dow88 due to stronger drug exchange property of the resin. In addition, the effect of increased amounts of resin and delayed drug release could be expressed as slowed kinetic constant ($k$) for matrices containing Dow88.

Drug release from EC-based matrices containing Dow88 is shown in Fig. 7. During the release test, it was observed that Dow88 caused non-swelling EC-based matrices to disintegrate with a disintegration rate and extent paralleling the amount of embedded resin added to the matrix. This observation was further quantitatively confirmed by a disintegration test. Clearly, disintegration times were shorter with increasing amounts of embedded resin, which were 329.6±4.4, 72.3±1.3, 8.3±0.5, 1.3±0.4, and 0.4±0.1 min for EC-based matrices containing 5%, 10%, 20%, 30%, and 40% Dow88, respectively. A greater disintegration rate allowed the drug to be released faster (Fig. 7) due to an increase in surface area exposed to the medium (24). However, the amount of drug released into solution tended to be lower because the released drug was bound to resin dispersed in the medium. The decrease in the amount of drug released into solution was more pronounced as the amount of dispersed resin, and hence, resinate formation in the medium increased. This result was in agreement with previous studies where Am69 was embedded into EC-based matrices (11).

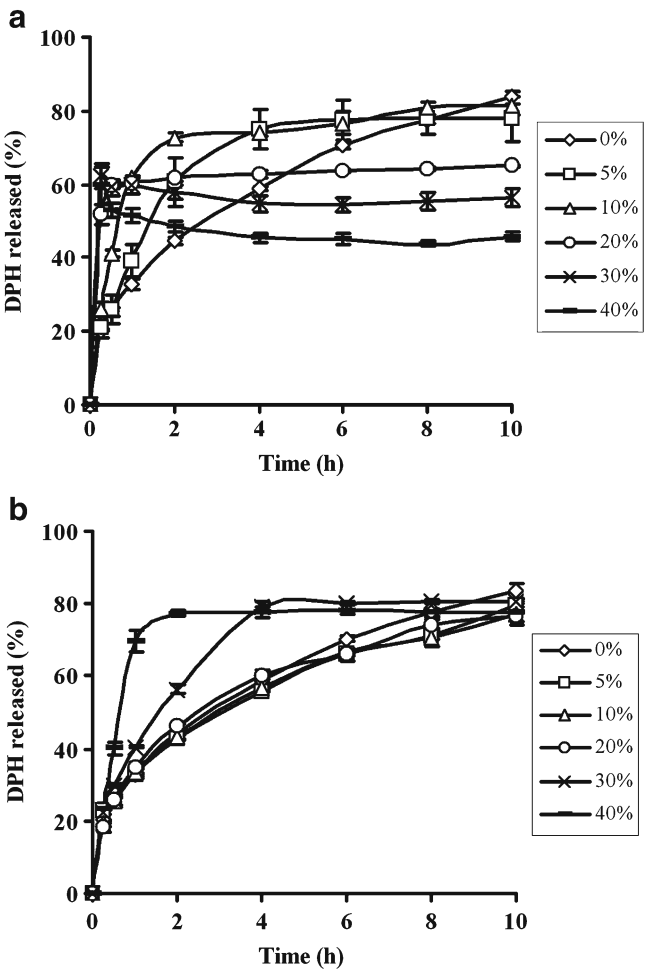


**Fig. 7.** DPH release from EC-based matrices containing various amounts of **a** Dow88 and **b** Am64, respectively

The mechanism of matrix disintegration due to embedded resin was further evaluated. It was believed that resins caused matrix disintegration via resin swelling; therefore, the swelling of resins was determined (10,11). The swelling of Am69 was also determined for comparison. Indeed, results indicated that the resins swelled volumetrically (volume swelling) and gravimetrically (weight swelling). The volume swelling was 19.6±3.1%, 44.0±2.9%, and 68.5±5.2%, while the weight swelling was 158.9±14.2%, 231.9±2.2%, and 167.2±5.4% for Dow88, Am64, and Am69, respectively. It could be found that the volume and weight swelling were not equal and not totally parallel. For example, the volume swelling of Am64 was lower than that of Am69, but the former resin had higher weight swelling than the latter resin. This result indicated that volume and weight swelling might have different origins. Volume swelling represented an increase in size (swelling action), whereas weight swelling indicated that water was adsorbed by the resin without a change in volume or size (wicking action) (25). Previous studies reported that the disintegrating effect of Am69 was primarily due to the adsorption of water and subsequent increase in resin size (10,11). However, Am69 is a gel-type resin with high volume and weight swelling. In this work, Dow88 had a weight swelling comparable to Am69 but significantly lower volume swelling. Both Dow88 and Am69 possess sodium sulfonate ion exchange sites, which are dissociable and have a high affinity for water. However, Dow88 is a macroporous resin that has a higher degree of crosslink than gel-type resins (20). Thus, Dow88 had a similar propensity for water adsorption to Am69; however, Dow88 swelled slightly. This result suggested that matrix disintegration created by embedded Dow88 might be the result of wicking (water adsorption) rather than swelling actions.

Figure 7 displays the drug release profiles of EC-based matrices containing Am64. Due to the hydrophobicity of EC, Am64 addition caused non-swelling EC-based matrices to disintegrate; however, the extent of matrix disintegration was significantly less than observed in Dow88. Matrices containing up to 20% Am64 disintegrated only slightly over 10 h, and the resultant drug release profiles did not differ significantly from those without the resin (Fig. 7). This result implied that the increase in drug release caused by disintegration was offset by the decrease in drug release due to drug exchange on the embedded resin. As the amount of the embedded resin increased from 30% to 40%, the extent of disintegration increased but was incomplete at 10 h, as confirmed by photographic observation (Fig. 6c). Nonetheless, a greater disintegration of these matrices allowed for an increase in drug release, which dominated the adsorption of the drug on ion exchange sites of the embedded resin. As a result, drug release was faster in matrices containing 30% to 40% Am64 than from resin-free matrices. However, the amount of drug released from the matrix was likely less than resin-free matrices due to drug exchange and resinate formation. Due to slow and incomplete disintegration, a portion of the drug was bound to resin dispersed in the medium or resided in the remaining matrices. The decrease in drug release caused by Am64 was not as pronounced as the decrease caused by Dow88 because of the weaker drug exchange property of Am64. Thus, the profiles of drug release from EC-based matrices containing 30% to 40% Am64 were similar to those containing up to 10% Dow88.

In general, it has been suggested in the literature that softer tablets disintegrate quickly, whereas harder tablets disintegrate more slowly. Therefore, pore structure is significant for tablet disintegration; softer tablets have larger pores and greater tortuosity, allowing for more water penetration and subsequent breakage of inter-particle binding and disintegration (4,5,25–27). Additionally, softer tablets have weaker inter-particle bonds that are more easily broken by disintegrating forces (3). EC-based matrices that contained increasing amounts of Dow88 had reduced hardness (Fig. 2b) and increased pore size, as observed in SEM results (Fig. 3d *versus* e). Therefore, the decrease in hardness of EC-based matrices containing Dow88 might contribute to increased disintegration. On the other hand, Am64 yielded harder EC-based matrices due to the high compressibility of the resin (Fig. 2b), which needed to be overcome by disintegrating forces derived from the resin. Moreover, EC-based matrices containing Am64 likely had smaller pores and greater tortuosity due to a denser powder bed (Fig. 3e *versus* f) that impeded water penetration into matrices. These factors outweighed the disintegrating forces caused by swelling and wicking (water adsorption) actions by Am64, leading to delayed matrix disintegration. Also, it explained that EC-based matrices containing Am64 did not disintegrate as much as those containing Dow88 even though Am64 displayed higher volume and weight swelling.

## Drug Release from Matrices Under Simulated Gastrointestinal Conditions

According to the above results, resins had the potential to slow down drug release from HPMC-based matrices. EC-based matrices containing either resin had a propensity for disintegration; thus, these matrices could not be used to delay drug release. Therefore, the drug release of selected HPMC-based matrices containing Dow88 or Am64, as well as resin-free matrices, was further investigated under simulated gastrointestinal conditions. Drug release from resin-free matrices under simulated gastric conditions was lower than

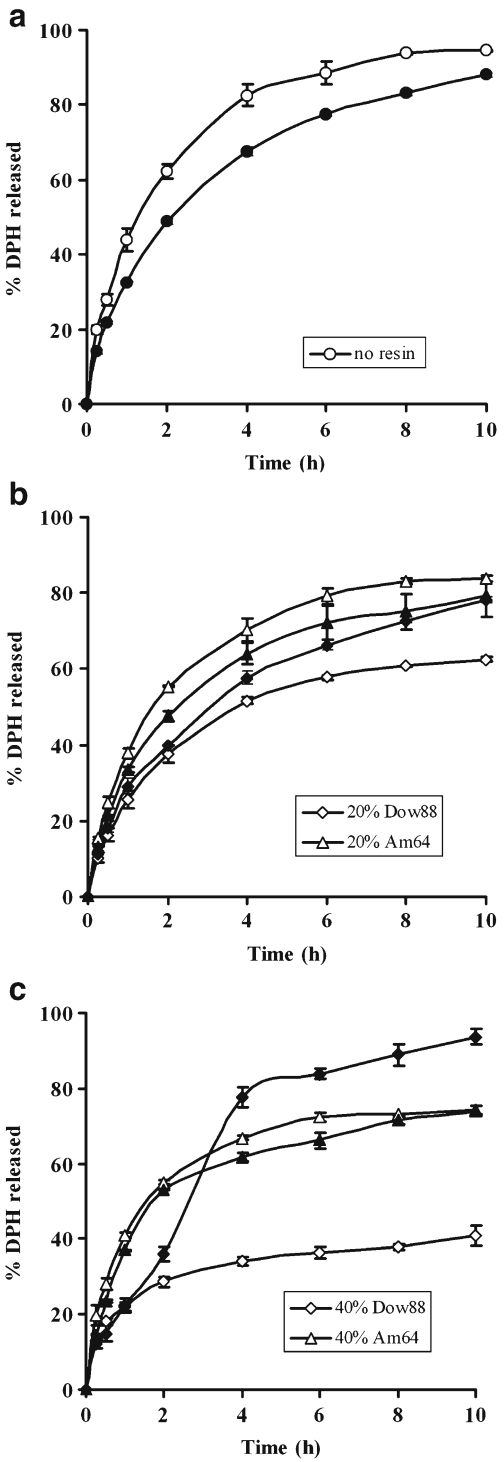


**Fig. 8.** DPH release from HPMC-based matrices containing **a** no resin, **b** 20%, and **c** 40% each resin tested in deionized water (*open symbols*) and under simulated gastrointestinal conditions (*filled symbols*), respectively

in deionized water (Fig. 8a). This result might be due to a salting-out effect caused by inorganic salts, which decreased polymer swelling and erosion, thus delaying drug release (7,8). This explanation was supported by photographs (Fig. 6) in which the gelled matrices under simulated gastrointestinal conditions were more persistent than in deionized water during drug release. Results revealed that Dow88 did not retard drug release under simulated gastrointestinal conditions as much as in deionized water, especially when the amount of embedded resin was high (Fig. 8b, c). This result might be due to competition between counter ions and the drug for binding sites on the embedded resin (10,11). Thus, more drug was available due to a decrease in free binding sites and was released from the matrices into solution. Matrices containing a higher amount of embedded resin provided a higher drug release because these matrices contained a lower amount of matrix former. Thus, the free drug was released faster from the resultant matrix gel (5). In addition, the drug released in the buffer stage (2–10 h) was markedly higher than the amount released in the acidic stage (0–2 h). This was because $Na^+$, apart from $H^+$, was present in the buffer stage, which had a higher affinity for strongly cationic exchange resins, such as Dow88, compared to $H^+$ (20). Additionally, the total amount of cations in the buffer stage (150 mEq of $Na^+$ plus 75 mEq of $H^+$) was three times higher than in the acidic stage (75 mEq of $H^+$). Cations in the buffer stage could compete with the drug to a greater extent for binding sites on the resin (28). In contrast, drug release from matrices containing Am64 in deionized water was higher than under simulated gastrointestinal conditions, in which both $H^+$ and $Na^+$ were present (Fig. 8b, c). This result suggested that both $H^+$ and $Na^+$ could slightly compete with the drug in binding to the resin under simulated gastrointestinal conditions. Therefore, the increase in drug release caused by competition with cations was minor and was dominated by a decrease in drug release due to the salting-out effect of the polymer, thus providing a lower drug release under simulated gastrointestinal conditions. As shown in Fig. 8a–c, drug release from the matrices continuously decreased as the amount of Am64 increased. Thus, Am64 could retard drug release under simulated gastrointestinal conditions.

## CONCLUSION

Dow88 and Am64 yielded matrices with unique physical properties. Dow88 caused the matrices to become softer, resulting in an increase in thickness, diameter, and friability. In contrast, Am64 increased matrix hardness and yielded a thickness, diameter, and friability similar to resin-free matrices. The addition of Dow88 decreased drug release from HPMC-based matrices in deionized water more than Am64. However, Am64 impeded drug release under simulated gastrointestinal conditions. EC-based matrices containing either resin had a propensity for disintegration caused by swelling and wicking (water adsorption) actions by the resin.

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