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Research Article

Effect of a Pharmaceutical Cationic Exchange Resin on the Properties of Controlled Release Diphenhydramine Hydrochloride Matrices Using Methocel K4M or Ethocel 7cP as Matrix Formers

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Abstract. This work was aimed at evaluating the effect of a pharmaceutical cationic exchange resin (Amberlite IRP-69) on the properties of controlled release matrices using Methocel K4M (HPMC) or Ethocel 7cP (EC) as matrix formers. Diphenhydramine hydrochloride (DPH), which was cationic and water soluble, was chosen as a model drug. HPMC- and EC-based matrices with varying amounts (0–40%*w*/*w*) of resin incorporation were prepared by a direct compression. Matrix properties including diameter, thickness, hardness, friability, surface morphology and drug release were evaluated. The obtained matrices were comparable in diameter and thickness regardless of the amount of resin incorporation. Increasing the incorporated resin decreased the hardness of HPMC- and EC-based matrices, correlating with the degree of rupturing on the matrix surfaces. The friability of HPMC-based matrices increased with increasing the incorporated resin, corresponding to their decreased hardness. In contrast, the EC-based matrices showed no significant change in friability in spite of decreasing hardness. The incorporated resin differently influenced DPH release from HPMC- and EC-based matrices in deionized water. The resin further retarded DPH release from HPMC-based matrices due to the gelling property of HPMC and the ion exchange property of the resin. In contrast, the release from EC-based matrices initially increased because of the disintegrating property of the resin, but thereafter declined due to the complex formation between released drug and dispersed resin via the ion exchange process. The release in *ionic solutions* was also described. In conclusion, the incorporated resin could alter the release and physical properties of matrices.

KEYWORDS: diphenhydramine hydrochloride; ethylcellulose; hydroxypropylmethylcellulose; ion exchange resin; matrix properties.

INTRODUCTION

Manipulation of polymers as matrices has been a popular mean to control release of drugs (1,2). Matrices can be prepared via direct compression or a wet granulation process (2–7). Materials generally used in forming matrices are polymers, which can be organized into hydrophobic and hydrophilic groups. Drug release from matrices using hydrophobic (water insoluble) polymers such as ethylcellulose derivatives proceeds via diffusion through an almost intact matrix (3). On the other hand, matrices made of hydrophilic polymers such as hydroxypropylmethylcellulose derivatives swell and form a gelled matrix upon contact with water, and thus drug release is primarily governed by diffusion through the gelled matrix (4). Polymers selected from either the same or different groups can be admixed to modify the rate and mechanism of drug release from matrices (2,3). In addition, drug release from matrices may be tuned by adjustment of polymer concentration or/and addition of other excipients (3–8).

Aside from the desired release, the physical properties of matrices are also of great importance. Finished matrices must have acceptable physical properties, typically hardness and friability, which can withstand impacts and abrasions during storage, transportation and handling. Matrices failing to meet the physical requirements could break or partially disintegrate, which may cause dose-dumping after administration (9). Using the above techniques to modify the drug release may also alter the physical properties of matrices (1).

Ion exchange resins are swellable crosslinked copolymers which can reversibly adsorb ionized drugs via ion exchange. The resins have been primarily used as drug carriers for the development of controlled release systems, and as taste maskers in preparations of suspensions and chewing gums of bitter drugs. Furthermore, resins with a high propensity for swelling can act like a disintegrant, usable in tablet formulations (10,11). Recently, it was found that the direct compression of some resins with other matrix components can modify drug release from matrices without need for prior formation of resinate (4). Nevertheless, knowledge of this extended use of resins remains scant, and must be further investigated not only with regard to the modification of the drug release but also the alteration of the physical properties of matrices. Therefore this study was aimed at investigating the effect of a

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pharmaceutical cationic exchange resin (Amberlite IRP-69) on the physical and release properties of controlled release matrices using Methocel K4M (HPMC) or Ethocel 7cP (EC), which represents hydrophobic and hydrophilic polymers respectively, as matrix formers. In this work, diphenhydramine hydrochloride (DPH), an antihistamine agent, was chosen as a model drug. It is well absorbed from the gastrointestinal tract. Because of its short half life (approximately 5–6 h), the usual dose of DPH (10–50 mg) is orally taken four times daily (12,13). The drug therefore could potentially be prepared in controlled-release matrices which provided better convenience and patient compliance.

MATERIALS AND METHODS

Materials

Amberlite IRP-69 (Sigma Chemical Co., USA), Diphenhydramine hydrochloride (Beijing Shuanglao Pharmaceutical Co., China) and Potassium chloride (Ajax Finechem, Australia) were purchased from various suppliers. Methocel K4M and Ethocel 7cP were kindly donated from Colorcon Ltd., UK. Magnesium stearate (BP grade) was a gift from Glaxo Wellcome Vidhyasom, Thailand. Deionized water (DI) prepared by a water purifier (Barnstead/Thermolyne D 4745, USA) was used entirely in this work.

Methods

Preparation of Matrices by Direct Compression

The formulations and compositions of prepared matrices are presented in Table I. Required compositions were blended together for 10 min, and then each portion (100 mg) was weighed accurately and fed into a hydraulic hand press machine (Specac P/N 15011/25011, UK). All matrices were compressed using stainless steel flat-circular punches (6.35 mm in diameter) with a constant force of 5 tons for 5 s of dwelling time. One hundred matrices were prepared for each batch of the formulations. The matrices obtained were kept in tight containers until used.

Diameter and Thickness of Matrices

Ten matrices of each formulation were randomly selected and then measured for their diameter and thickness using a micrometer (S229, Sylvac, Switzerland).

Table I. Formulations and Compositions of Prepared Matrices

Formulations	HPMC or EC					
Compositions (%*w*/*w*)	/0	/5	/10	/20	/30	/40
DPH	30	30	30	30	30	30
Amberlite IRP-69[a]	0	5	10	20	30	40
Magnesium stearate	1	1	1	1	1	1
HPMC[b] or EC[c] added to	100	100	100	100	100	100

[a] The resin incorporated
[b] Methocel K4M
[c] Ethocel 7cP

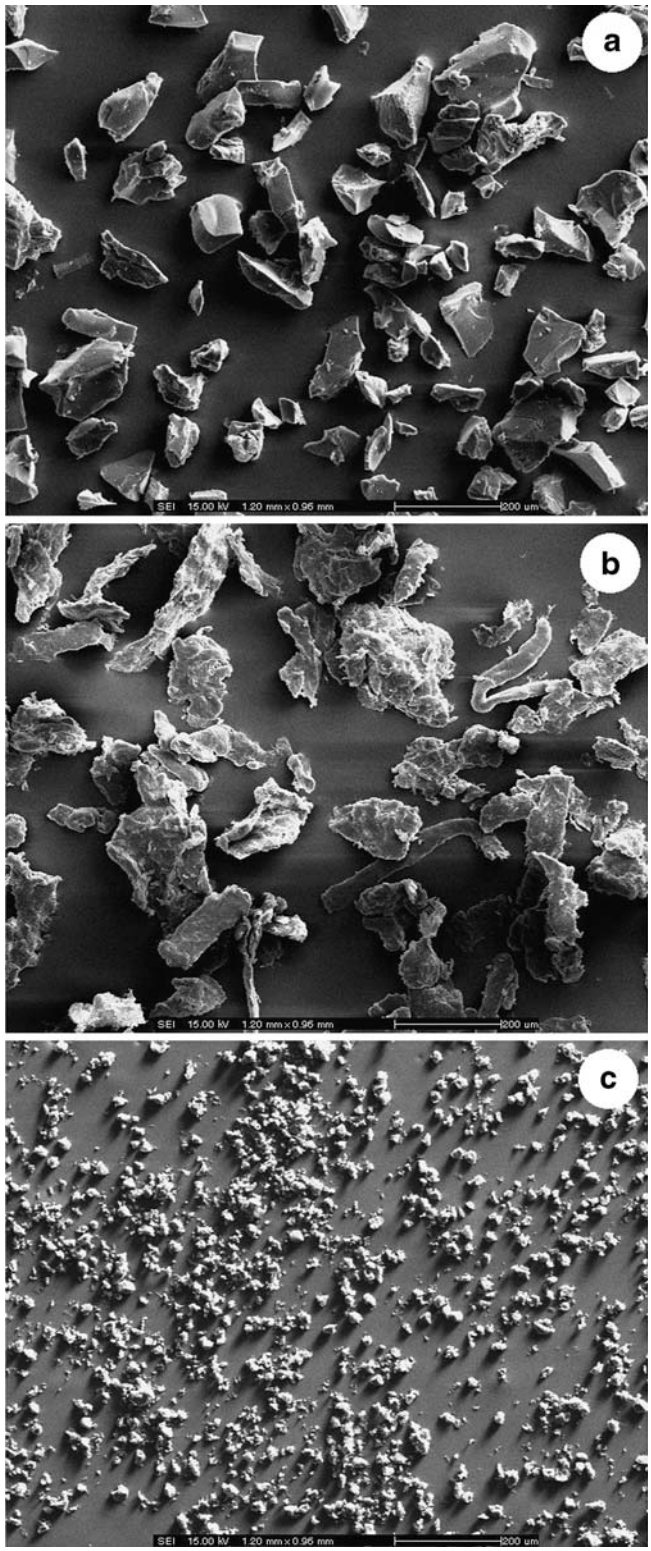

Fig. 1. Scanning electron micrograph of **a** Amberlite IRP-69, **b** Methocel K4M (HPMC) and **c** Ethocel 7cP (EC)

Hardness of Matrices

The hardness of ten matrices was measured using a texture analyzer (Stable Micro Systems TA.XT plus, UK). The measurement was carried out in a manner that the matrices were pressed by a stainless steel flat-face (6 mm in diameter)

cylindrical probe moving at a predetermined speed (1 mm/s). The hardness value, directly read from the instrument, was the maximum force that caused a diametrical crush of matrices.

Friability of Matrices

Twenty matrices were weighed (W_1) and rotated for 100 revolutions in 4 min in a Roche friabilator. The matrices were then weighed (W_2) again, and the friability was calculated as the percent weight loss of tested matrices using (14,15).

$$\left(\frac{W_1 - W_2}{W_1}\right) \times 100 \quad (1)$$

Drug Release

Drug release was investigated in triplicate using a USP release testing apparatus I (Prolabo Dissolutest, France) (16). The release medium was 900 ml of deionized water or ionic solutions (i.e. KCl solutions (0.005–0.4 M), simulated gastric (SGF) and intestinal fluids USP without enzyme (SIF)), as indicated. The rotation and temperature were maintained at 50 rev/min and 37±1°C, respectively, throughout testing. At predetermined times, small portions (5 ml) of medium were withdrawn through a filter and assayed by an ultraviolet spectrophotometer (Lambda 2, Perkin-Elmer, Germany) at a wavelength of 218 nm. The same volume of fresh medium was returned into the vessels to keep the volume constant. Photoimages of matrices during the release test were also determined. The matrices were conducted in the same condition of the release test. At predetermined times, the matrices were taken out and then viewed using a digital camera and associated image analysis software (QX5, Digital Blue, China) under a fixed magnification.

Disintegration Test

The disintegration time was measured using a USP disintegration testing apparatus (Sotax DT3, Switzerland) (16). Six matrices were placed into a basket-rack assembly at the start of each test. The medium used for this test was deionized water or the ionic solutions, as indicated, which were maintained at 37±1°C throughout testing. The disintegration time, defined as the point at which matrices disintegrated and passed through the screen of the assembly, was recorded.

Scanning Electron Microscopy (SEM)

The resin, polymers and surface morphology of produced matrices were viewed by an electron scanning electron microscope (CamScan MX 2000, UK). Prior to testing, samples were fixed on stubs and sputter coated with gold in a vacuum evaporator (Cressington Sputter Coater 108, UK). Visualization was performed at a fixed magnification (shown in SEM pictures).

RESULTS AND DICUSSION

Amberlite IRP-69

This resin is a strongly cationic exchange resin commercially produced in plate-like particles (Fig. 1a) with a reported average diameter of 165 μm (17). The resin structure is a crosslinked styrene-divinylbenzene copolymer carrying many fixed salts of sodium sulfonate (RSO_3Na; R is the copolymer). Though completely water-insoluble, when placed in aqueous solutions the resin hydrates and swells considerably due to the hydrophilicity and dissociation of the sodium sulfonate salts. The sodium ion of the sulfonate salt is able to be exchanged for, or be replaced by, a counter-ion or a cationic drug in the external solution.

Effect on Physical Properties

Direct compression was used to prepare matrices due to ease of production and to avoid using solvents and heat (15,18). All matrices obtained were of fairly uniform weight (%CV ≤ 1), since the blended compositions were weighed and then carefully fed to the compress (15). In each polymer-based system, the matrices were comparable in diameter and thickness regardless of the amount of resin incorporated. The average diameter of each formulation was in the range of 6.40–6.41 (%CV ≤ 1.59) for HPMC- and 6.40 (%CV ≤ 0.00) mm for EC-based matrices, respectively. The diameter was slightly larger than that of the punches used (6.35 mm), probably due to the elastic recovery of matrices (19). The average thickness of each formulation was in the range of 2.80–2.98 (%CV ≤ 2.54) for HPMC- and 2.64–2.84 (%CV ≤ 0.96) mm for EC-based matrices, respectively. The diameter of matrices using EC was slightly lower than those using HPMC, which might be attributed to the smaller particle size and hence greater compressibility of EC.

With regard to matrices without the resin, the hardness of HPMC/0 was much lower than that of EC/0 (Fig. 2). In SEM pictures, HPMC/0 (Fig. 3a) had a lesser compact surface than EC/0 (Fig. 4a), in agreement with the observed hardness. This was attributed to the fact that EC had a much smaller particle size than HPMC (Fig. 1b,c). Particle size was one of the most important factors controlling the hardness of compressed tablets or matrices, especially when plastic materials were used as tablet fillers or matrix formers. A smaller particle size was associated with a greater bonding surface area and hence

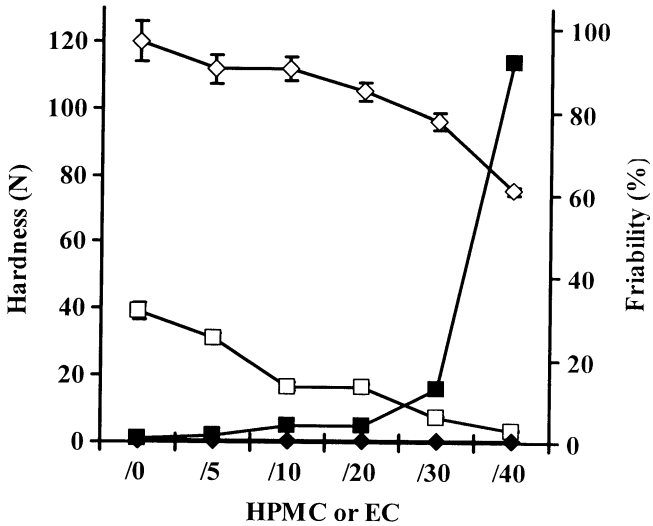

Fig. 2. Hardness (*opened symbols*) and friability (*closed symbols*) of various (*square*) HPMC- and (*diamond*) EC-based matrices

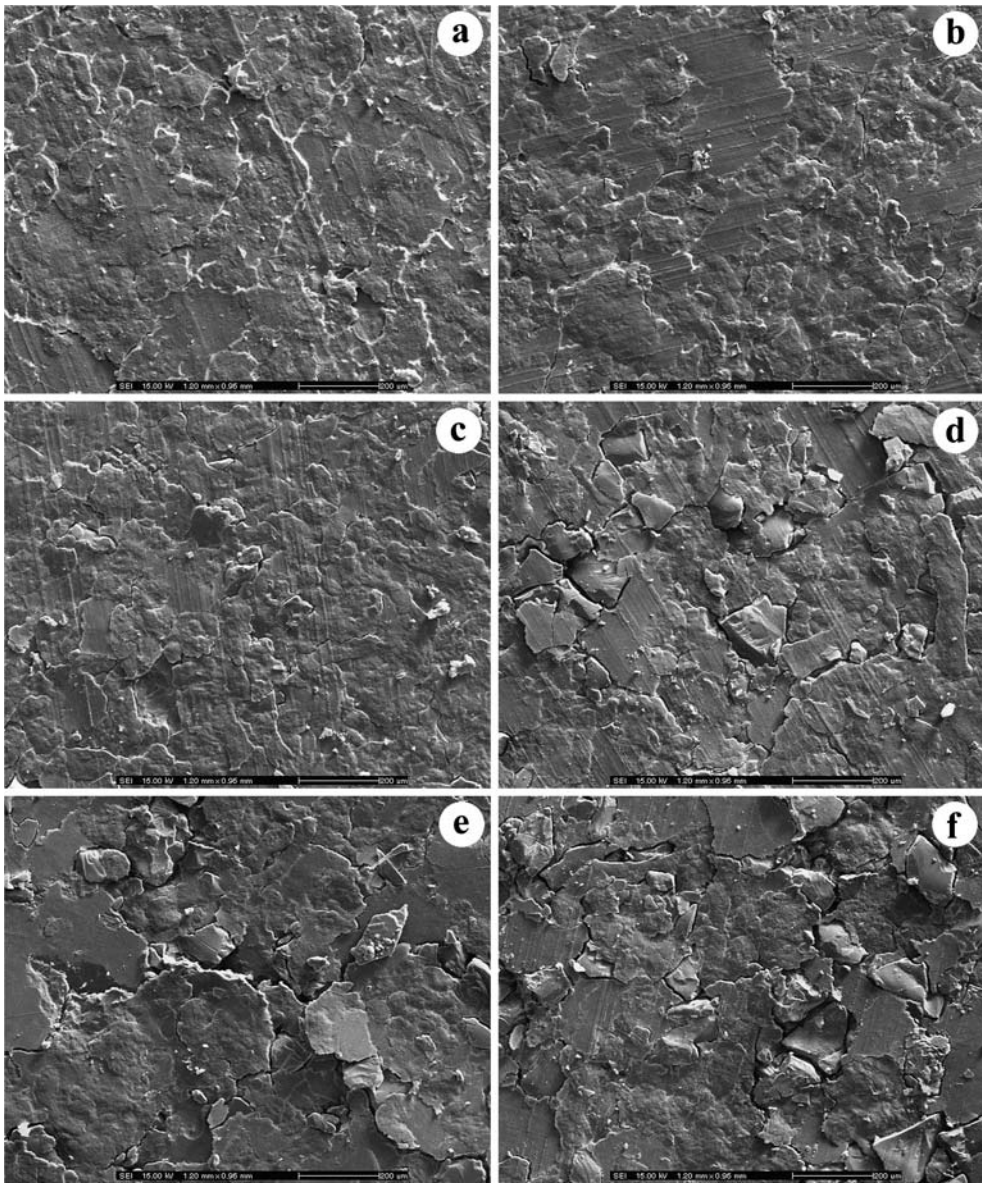

Fig. 3. Surface morphology of HPMC-based matrices; **a** HPMC/0, **b** /5, **c** /10, **d** /20, **e** /30 and **f** /40, respectively

numbers of interparticular attractions among contacting excipients, thus providing greater compact and hardness of tablets or matrices (3,20). HPMC and EC could be used as directly compressible matrix formers for preparing controlled release matrices. Previous investigations reported that both polymers had good compressibility without mention of which was superior. During compression, the polymers primarily underwent plastic deformation, forming matrices whose hardness increased with decreasing particle size (3,18,19).

Resin incorporation significantly reduced the hardness of HPMC- and EC-based matrices. The reduction of hardness increased with increasing amounts of resin incorporation (Fig. 2). This finding agreed with the SEM results in which ruptures on the surface of matrices appeared progressively in proportion with increasing resin incorporation (Fig. 3b–f and Fig. 4b–f). This could be explained by the results of further study. For these experiments, direct compression of the resin alone was performed, in which it was found that the resin could not form matrices due to extremely low hardness. This demonstrated the poor cohesive attraction and hence poor compressibility of the resin. From careful consideration of Fig. 3b–f and Fig. 4b–f, it could be seen that partial or total ruptures occurred along interfaces of the incorporated resin. This evidence could also imply the poor adhesive attraction between the resin and other components. Therefore, the hardness of matrices would decrease as the incorporated resin was increased. This finding was similar to previous works in which the incorporation of resinates (dextromethorphan-loaded resins) or cellulose acetate butyrate coated resinates (phenylpropranolamine-loaded resins) resulted in a dramatic decrease in the hardness of matrices (17,21).

An increase in friability was one of the most common consequences of decreasing the hardness of tablets. With HPMC-based systems, the friability increased with increasing amounts of resin incorporation in a manner that could be divided into two phases. In the first phase, the friability

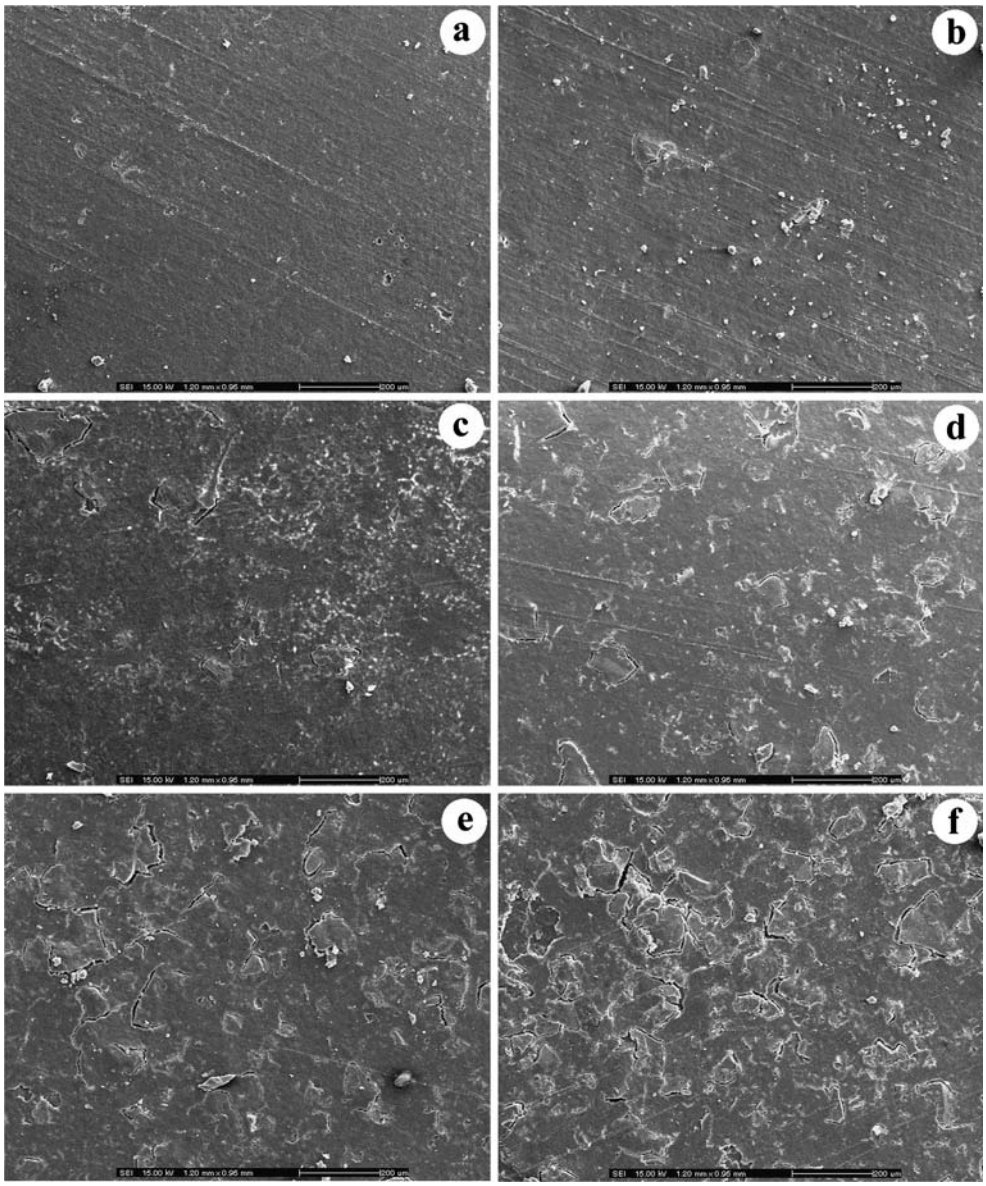

Fig. 4. Surface morphology of EC-based matrices; **a** EC/0, **b** /5, **c** /10, **d** /20, **e** /30 and **f** /40, respectively

increased gradually from 0.88 to 3.94% as the matrices contained up to 20% resin, corresponding to a decrease in hardness from 39.1 to 16.7 N (Fig. 2). The friability increased quickly (from 3.94 to 92%) in the second phase, in which the hardness of matrices containing 20 to 40% resin dropped from 16.7 to 3.7 N. In contrast, the friability of EC-based matrices containing up to 40% incorporated resin was totally unchanged (0.21–0.45%) although their hardness decreased from 120 to 76 N (Fig. 2). It should be noted that all matrices using EC had greater hardness than those using HPMC. The results suggested that there was a critical matrix strength under which the friability would increase in relation to the decreased hardness, otherwise remaining unchanged. The critical matrix strength of HPMC-based matrices might be about 16–17 N, below which the friability increased greatly. With EC-based matrices, the friability was considerably unchanged because the hardness might be above their critical matrix strength. Our findings were in agreement with a previous result in which the friability of matrices (0.6–1%)

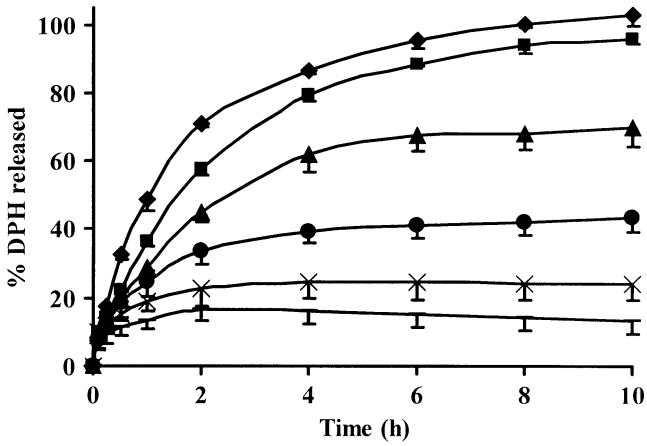

Fig. 5. DPH release from (*filled diamond*) HPMC/0, (*filled square*) /5, (*filled upright triangle*) /10, (*filled circle*) /20, (*ex symbol*) /30 and (*horizontal bar*) /40, respectively. One-side *error bars* were presented for clarification, and some were hidden by bigger symbols

did not considerably change in spite of a dramatic decrease in hardness from 105 to 60 N (22).

Effect on Drug Release in DI

DPH was very soluble in water (1 g/ml), dissolving very fast (<1 min) (23). Without the resin, development into matrices using either HPMC or EC retarded *in-vitro* release of DPH (HPMC/0 in Fig. 5 and EC/0 in Fig. 6). The mechanism of DPH release from these two matrices was different because of the distinct natures of the matrix formers. HPMC was a hydrophilic gelling polymer. Upon contact with water, HPMC/0 formed a gelled matrix through which DPH diffused (Fig. 7). The gelled matrices still persisted after 100% release reached, demonstrating that the DPH release from HPMC/0 was predominantly governed by drug diffusion through rather than erosion of the gelled matrix (4). On the other hand, EC/0 provided a non-gelling matrix that remained intact throughout the release test (Fig. 7) due to the hydrophobicity of the matrix former (EC). Therefore, the DPH release from EC/0 proceeded via diffusion through water-filled pores created by the leaching out of dissolved drug (3). Though governed by different mechanisms, it could be clearly seen that HPMC/0 provided faster DPH release than EC/0 (Fig. 5 and Fig. 6). The hydration and gelling of HPMC was quite fast, resulting in the rapid gelling formation of HPMC/0 (8,24). As mentioned earlier, DPH dissolved freely in water, allowing it to diffuse and be rapidly released from the gelled matrix of HPMC/0. In contrast, EC/0 had a lower affinity for water, thus resulting in the slower rate of DPH release (25).

The influence of the resin on DPH release from HPMC-based matrices is shown in Fig. 5. In comparison with the matrices without the resin (HPMC/0), the incorporation of the resin further lowered DPH release. This was due to both the gelling effect of the polymer and the ion exchange effect of the resin (4). Upon contact with DI, the matrices quickly formed the gelled matrix (Fig. 7) in which DPH simultaneously dissolved and then diffused out. During diffusion through the gelled matrix containing the resin, the dissolved drug (DPH) was partly released but was also exchanged for sodium ions (Na) in the resin, forming a drug–resin complex by the following exchange reaction:

$$RSO_3Na + DPH^+ \Leftrightarrow RSO_3DPH + Na^+ \quad (2)$$

In the complex, the drug bound with the sulfonic group of the resin by electrostatic attraction, and was not liberated unless it was replaced by another counter ion (11). Since there were no counter ions in DI, only the limited amount of drug remaining unbound was available for release, thus explaining the lesser amount of released drug.

As shown in Fig. 5, the DPH release decreased with increasing amounts of resin incorporation. This could be explained by applying equilibrium principles to Eq. 2 (26). As the amount of the resin was increased, the reaction was driven to the right. This reaction was unlikely to reverse in this situation because of the lack of counter ions in DI, resulting in a more formation of the drug–resin complex and hence a lesser DPH release. Indeed, this finding partly agreed with a previous result (4). In that case, drug release was found to decrease as resins were added to a certain point, beyond which it remained unchanged. In this study, the DPH release continuously decreased with increasing amounts of the incorporated resin due to increased complex formation, as described above. Moreover, the DPH release from matrices containing more than 30% resin (HPMC/30 and /40) decreased considerably from the plateau it had reached. Qualitatively speaking, the post-plateau release of HPMC/40 also appeared to decrease more quickly than that of HPMC/30. This finding suggested that some of the drug released in the medium was diffused back, exchanged for Na in the resin and then formed the drug–resin complex in the gelled matrix. This phenomenon occurred because the amount of incorporated resin, especially in HPMC/40, was excessive for the dissolved drug not yet released from the gelled matrix. Therefore, it was able to bind the released drug returning into the gelled matrix via diffusive gradient created by the exhaust of drug due to earlier complex formation. The matrices containing less than 30% resin (HPMC/5-/20) showed no decline in the plateau of drug release because the amount of incorporated resin was low, and thus reached equilibrium without needing to bind the released drug from the medium further.

As observed in Fig. 7, the gel formation, at least in the initial phase (e.g. 5 min), of the matrices with the resin (e.g. HPMC/20) appeared faster than that without the resin (HPMC/0). This was probably resulted from the hydrophilic property of the incorporated resin promoting the matrix hydration. However, the release from the matrices with the resin was lower than that without the resin, as shown in Fig. 5. This suggested that the effect of such different gelling, on the release, was minor compared with that of the ion exchange.

The EC-based matrices without the resin (EC/0) did not form the gelled matrix, and remained intact throughout the release test. The incorporation of the resin caused EC-based matrices to disintegrate (Fig. 7), resulting in completely different DPH release profiles compared to HPMC-based systems (Figs. 5 and 6). The matrix disintegration time decreased as the resin incorporation increased (Fig. 8). This finding demonstrated that the resin (Amberlite IRP-69) could act as a disintegrant, as previously found with other resins, e.g. Amberlite IRP-88 and Indion 414 (4,10,27). The disintegration

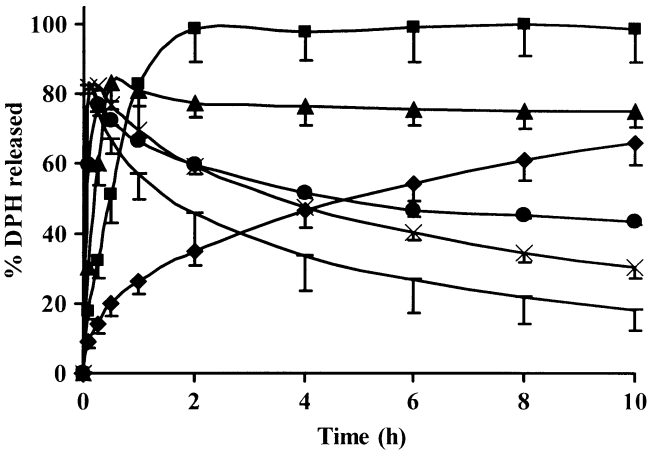

Fig. 6. DPH release from (*filled diamond*) EC/0, (*filled square*) /5, (*filled upright triangle*) /10, (*filled circle*) /20, (*ex symbol*) /30 and (*horizontal bar*) /40, respectively. One-side *error bars* were presented for clarification, and some were hidden by bigger symbols

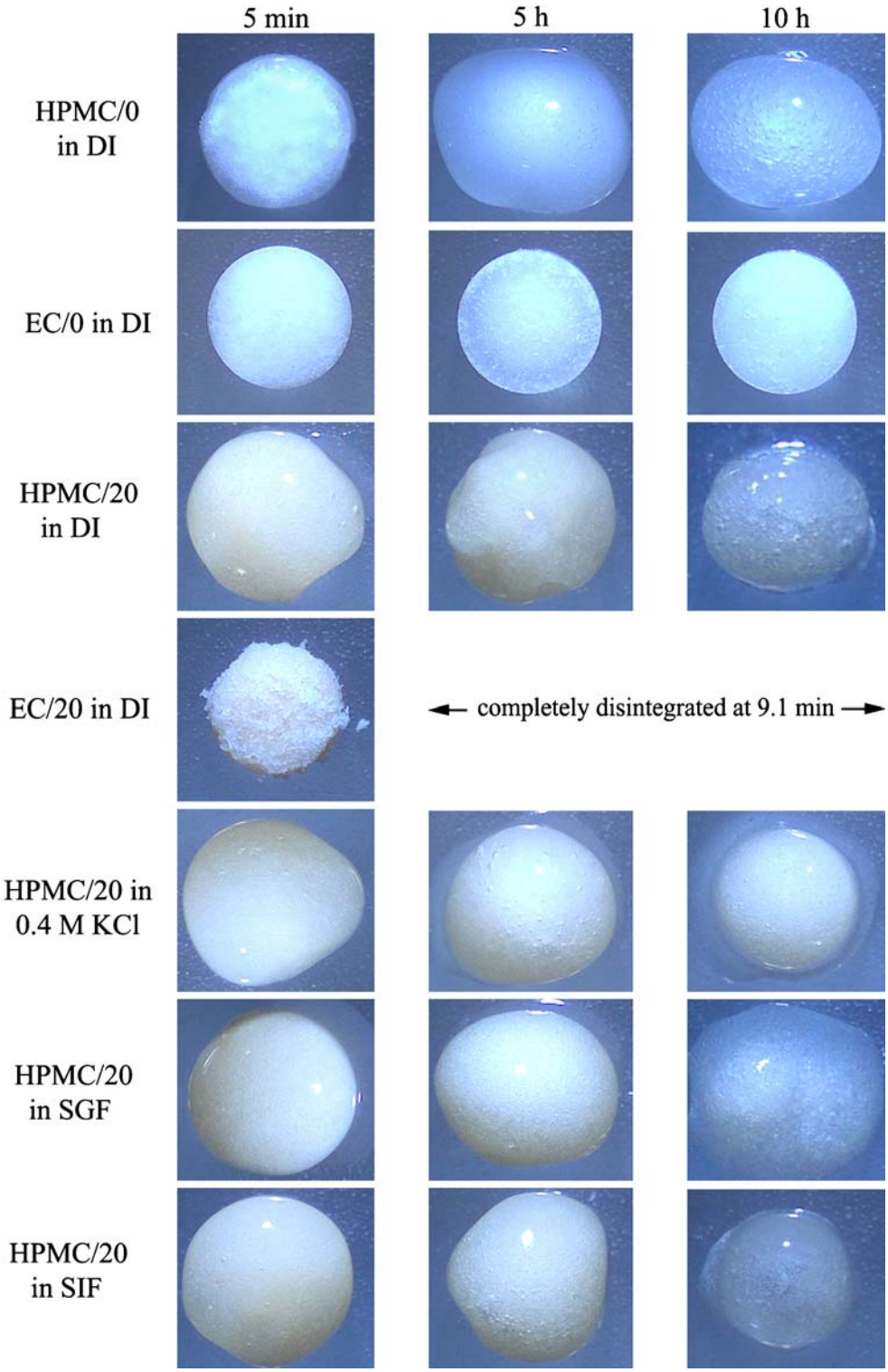

Fig. 7. Photoimages of matrices during the release test in different media

mechanism for these resins was associated with their swelling ability. Upon exposure to water, the resins first swelled and then expanded, disintegrating the matrices they incorporated. This study informed that it should be aware of the propensity for disintegration and hence dose-dumping prior to incorporation of a resin in matrices designed to control drug release from a wholly single unit in the gastrointestinal tract.

In the matrices with 5% resin (EC/5), the DPH release was higher than that from the matrices without the resin (EC/0). This was attributed to the disintegration of matrices via swelling of the incorporated resin. It was observed that the rate of DPH release before its disintegration time (46 min) was also faster, indicating the occurrence of ruptures promoting drug release before complete disintegration of the matrices.

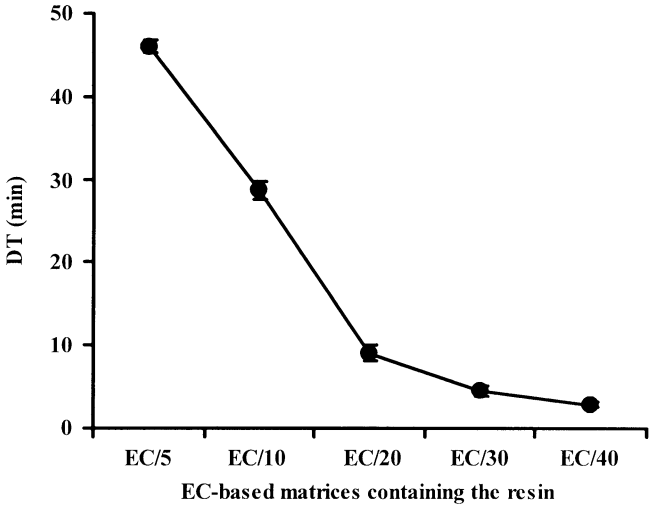

Fig. 8. Disintegration time (*DT*) of various EC-based matrices containing the resin. Some *error bars* were hidden by bigger symbols

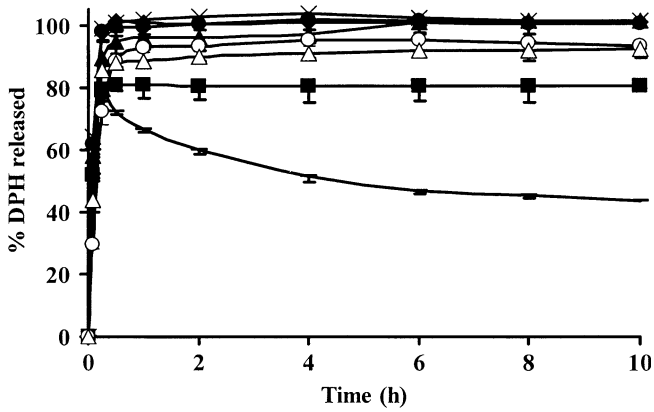

Fig. 10. DPH release from EC/20 in (*horizontal bar*) DI, (*empty circle*) SGF, (*empty upright triangle*) SIF, (*filled square*) 0.005, (*filled upright triangle*) 0.05, (*ex symbol*) 0.1, (*filled circle*) 0.2 and (*filled diamond*) 0.4 M KCl, respectively. One-side *error bars* were presented for clarification, and some were hidden by bigger symbols

The release was almost complete (98–100%) around 1–2 h, long after disintegration was complete. This suggested that the matrices had disintegrated into fractions from which the drug continued to release.

Faster disintegration did not always result in greater DPH release from EC-based matrices containing the resin. Incorporation of 10% or more resin into the matrices (EC/10-/40) typically resulted in biphasic release profiles, in which the release initially increased but thereafter declined (Fig. 6). This behavior was caused by the ion exchange property in addition to disintegrating property of the incorporated resin. Initially, the release increased rapidly due to the combined contributions of the rapid disintegration of the matrices and the rapid dissolution of the drug. This initial release tended to be faster when the incorporated resin was increased, resulting from faster and greater disintegration of the matrices (Figs. 6 and 8). It was likely that the matrices with higher amounts of the incorporated resin disintegrated into smaller fractions than those with lesser amounts, allowing for more efficient drug release due to a higher surface area. However, the release did not reach 100%, and later declined because the released drug was partly exchanged for Na in the dispersed resin and then formed the drug–resin complex. The bound drug could not release due to the absence of counter ions in the medium, resulting in the decreased drug release. This reduction of drug release was more pronounced as the amount of the resin incorporated in the matrices was increased, which was attributed to the equilibrium treatment described earlier.

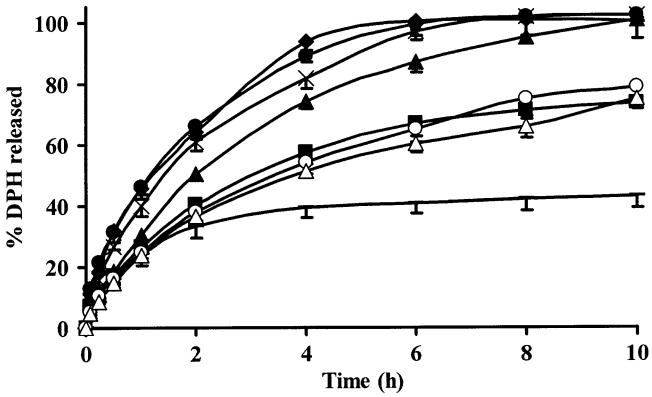

Fig. 9. DPH release from HPMC/20 in (*horizontal bar*) DI, (*empty circle*) SGF, (*empty upright triangle*) SIF, (*filled square*) 0.005, (*filled upright triangle*) 0.05, (*ex symbol*) 0.1, (*filled circle*) 0.2 and (*filled diamond*) 0.4 M KCl, respectively. One-side *error bars* were presented for clarification, and some were hidden by bigger symbols

Effect on Drug Release in Ionic Solutions

In regard to ion exchange resin-based dosage forms, ions played an important role in drug release (23,28). Therefore, DPH release from matrices containing 20% resin (HPMC/20 and EC/20) were further investigated in 0.005–0.4 M KCl solutions. As expected, it was found that the presence of ions in the release medium greatly influenced the DPH release from both matrices (HPMC/20 in Fig. 9 and EC/20 in Fig. 10). The drug release in KCl solutions was higher than that in DI. This was possible because potassium ion (K) acted as a cationic counter ion, like the drug, and could exchange for Na in the resin. During the release and complex formation process, the released drug (DPH) therefore competed with K in exchange for Na in the resin, which then formed less of the drug–resin complex (Eq. 3), meaning that a larger amount of drug remained available for release. Even in cases where the drug–resin complex was already formed, the bound drug would be replaced by K and then liberated from the complex (Eq. 4), thus further promoting the release. As shown in Figs. 9 and 10, the increase in the concentration of KCl solutions dramatically increased the release. According to the equilibrium treatment of Eq. 3 and Eq. 4, the increased K could more effectively both deter the released drug (DPH) from forming the drug–resin complex and liberate the bound drug from the formed complex. Chloride ion (Cl^-), the anionic co-ion, was not involved in the cationic exchange of this resin and hence in these phenomena (29).

$$RSO_3Na + DPH^+ + K^+ \Leftrightarrow RSO_3(DPH/K) + Na^+ \quad (3)$$

$$RSO_3DPH + K^+ \Leftrightarrow RSO_3K + DPH^+ \quad (4)$$

The gastrointestinal fluids containing a number of ions, it was also worth determining how the release behaved in SGF and SIF. Like in KCl solutions, the drug release in the simulated gastrointestinal fluids was higher than that in DI (HPMC/20 in Fig. 9 and EC/20 in Fig. 10). This was due to the existence of cationic ions, i.e. the mixture of H and Na in SGF and the mixture of K, H and Na in SIF, which competed with the drug in the ion exchange process as explained above. The total cationic ions in SGF and SIF were reported to be 0.104 and 0.087 M, respectively (30); nonetheless, the release in these media was evidently lower than that in 0.1 M KCl solution. It has been reported that the order of the exchange affinity (selectivity) for the cationic ions to strong ion-exchange resins, e.g. Amberlite IRP-69, obeyed the Hofmeister series, i.e. K>Na>H (28,31). Therefore, it could be explained that, at the comparable total cationic ions, K alone competed with the drug in the ion exchange process (Eq. 3 and Eq. 4) more efficiently than the mixture of those cationic ions, thus providing the higher release. The release in SGF and SIF was also lower than even that in 0.05 M KCl solution, implying that K had much higher affinity to the resin than either H or Na. The drug release in SGF seemed to be higher than that in SIF due to two reasons. First, SGF had more total cationic ions than SIF. Second, the lower pH of SGF increased the ionization and hence solubility of the drug, a weakly basic drug, in the medium and therefore the drug release was more or less promoted (4,5). These coupling contributions dominated the greater selectivity of K present in SIF, resulting in the higher release in SGF.

Tested in the ionic solutions, HPMC/20 still provided sustained patterns of drug release due to the gel formation of matrices that similarly formed in DI (Fig. 7). The gelled matrices quickly formed, but still persisted after the release test (10 h) and even 100% release reached. The gelled matrices seemed to erode less in a higher concentration of the ionic solutions, e.g. 0.4 M KCl solution. The high concentration of ions caused the salting-out effect to the polymer, which subsequently reduced the erosion rate of the matrices, as discussed elsewhere (32). However, the higher concentration of the ionic solutions provided the higher release (Fig. 9) in spite of the lower matrix erosion obtained. These findings confirmed that the release was primarily governed by the diffusion and the ion exchange rather than the erosion process. EC/20 was still able to result in fast-release patterns (Fig. 10) because it also disintegrated in the ionic solutions. The disintegration time determined was comparable in DI and the ionic solutions (8.2–11.8 min).

CONCLUSION

The resin incorporation greatly influenced the hardness, friability and *in vitro* release properties of matrices. The degree and pattern of the influences, especially the release, depended on the amount of resin incorporation and the nature of matrix formers. The hardness of resin-incorporated matrices was decreased due to the poor compressibility of the resin. The matrices with high amounts of the resin could be weakened to the extent that severely deteriorated the matrix friability, e.g. HPMC/20-/40. In DI, the incorporated resin further retarded the drug release from the hydrophilic gelling matrices of HPMC by virtue of the ion exchange property of the resin. In contrast, the hydrophobic non-gelling matrices of EC disintegrated by virtue of the disintegrating property of the resin, initially resulting in a rapid release. The release however later declined due to the ion exchange property of the resin. The release tested in the ionic solutions appeared greater than that in DI since the cationic counter ions competed with the drug in the ion exchange process.

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