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RESEARCH PAPER

Influences of Osmotic Agents in Diffusion Layer on Drug Release from Multilayer Coated Pellets

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ABSTRACT

Nonpareil beads were coated with three different functional layers, namely inner chlorpheniramine maleate-loaded hydroxypropylmethylcellulose (HPMC, 4 mPa·s) deposition layer, middle HPMC (400 mPa·s) diffusion layer, and outer polyacrylic polymer (Eudragit RS30D) retention layer. The osmotic agents, including sodium chloride, glycine, citric acid, and disodium hydrogen phosphate, were incorporated in different amounts into the diffusion layer and the influences on drug release were studied. The osmotic agent competed with HPMC for imbibed water and subsequently caused more water influx owing to the osmotic pressure gradient. An appropriate amount of osmotic agent in the diffusion layer was necessary to exert its effect on retarding drug release. The osmotic effect on drug release was compromised with pellets at a higher coating level of the diffusion layer due to the extensive swelling and rupture of coat. The release parameters, including dissolution $T_{50\%}$ and mean dissolution time, showed linear relationship with osmolalities of osmotic agents studied. The effect of the osmotic agent in the diffusion layer played an important role in determining the unique multiphase drug release profiles, particularly in the initial phase of dissolution, and reduced with depletion of the osmotic agent in the later phase of dissolution.

Key Words: Osmotic agent; Drug release; Multilayer coating; Pellet.

INTRODUCTION

Coating is an important pharmaceutical process to produce controlled-release dosage forms. Multilayer coating can produce dosage forms with different coat types that act synergistically in controlling drug release. Hydroxypropylmethylcellulose (HPMC) and polyacrylic polymers are commonly used in tablet and pellet

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coating.[1] The HPMC polymer is highly swellable and water-soluble, and low viscosity grades of HPMC can sparingly control drug release and usually act as vehicles for depositing drugs. While HPMC of high viscosity grades can form a viscous gel layer for controlling drug diffusion, it is not widely used in the coating process due to technical difficulties. Moreover, unavoidable erosion of the HPMC coat usually causes faster drug release. Certain types of polyacrylic polymers such as Eudragit RS and Eudragit RL were developed for controlled-release dosage forms.[2] They are water-insoluble, swellable film formers based on neutral methacrylic acid esters with a small proportion of trimethylammonioethyl methacrylate chloride. Owing to the existence of positively charged quaternary ammonium groups in polymer molecules, an inert subcoat is sometimes needed for prevention of interaction of drugs with coating materials. The quaternary ammonium groups determine the swellability of the films and their permeability to water. Compared to Eudragit RL, Eudragit RS has a reduced content of quaternary ammonium groups, thus has poorer water solubility and swells less easily in water. Water-soluble drugs preferably diffuse through the relatively hydrophilic pathway composed of quaternary ammonium groups of polyacrylic polymer chains.

Osmotic pump systems have been utilized to drive drug delivery at a controlled and predetermined rate.[3] Besides simple diffusion, pore formation, and erosion release, osmotic driven delivery has been reported to contribute to the drug release from coated tablets or pellets.[4,5] The unique organic acid-induced sigmoidal release of theophylline from Eudragit RS-coated pellets was brought about by the osmotic pumping process.[4] Acetaminophene pellets (with or without osmotic agents) were coated with a semipermeable cellulose acetate membrane. After coming in contact with the aqueous environment, these pellets imbibed water osmotically, which resulted in a rapid expansion of the membrane leading to the formation of pores from where the drug released rapidly after a lag time.[5] The dissolution of a soluble core can greatly enhance the drug release from the nonpareil system coated with HPMC and ethylcellulose.[6] The swelling of the pellets coated with HPMC and ethylcellulose composite film is a result of water influx due to osmotic pressure.[7]

In our previous study,[8] chlorpheniramine maleate (CM) exhibited zero-order release kinetics from spheroids coated with an inner HPMC layer and an outer polyacrylic polymer layer. In the multilayer coated pellets of CM,[9] nonpareil beads were coated with three different functional layers, namely, drug-loaded HPMC deposition layer, HPMC diffusion layer forming the diffusion barrier, and Eudragit RS retention layer preventing the dissolution and erosion of the diffusion layer. A high osmotic pressure in the sucrose core, the weakness of the Eudragit layer, and the strong swelling of the HPMC layer caused the rupture of the pellet coat. However, the rupture of the pellet coat did not result in total failure of the coat. The swollen polymers around the point of rupture gradually sealed up the site of rupture, maintaining the diffusion barrier. Addition of sodium chloride in the diffusion layer markedly retarded burst release due to competition for imbibed water between sodium chloride and HPMC. The water-soluble drug CM in the deposition layer was released by diffusion through highly swellable HPMC layer and less swellable Eudragit layer. These multilayer coated pellets in the presence of osmotic agents in the diffusion layer showed a stronger ability in controlling drug release.[9] Factors affecting the HPMC layer and the Eudragit layer in terms of swelling, viscosity, thickness, and diffusivity influenced drug release. Particularly, sodium chloride in the HPMC diffusion layer played a critical role in retarding burst release.[9] The osmotic agent in the HPMC diffusion layer rendered its effect on drug release mainly by affecting the diffusion layer. The difference in osmotic pressure between the diffusion layer and the external environment also affected drug release. This paper will further investigate the effects of different amounts and types of osmotic agents in the diffusion layer on drug release from multilayer coated pellets of chlorpheniramine maleate.

MATERIALS AND METHODS

Materials

Chlorpheniramine maleate [CM, British Pharmacopoeia (BP) grade] was used as a model drug. All the osmotic agents (AR grade) including sodium chloride, glycine, citric acid monohydrate, and disodium hydrogen phosphate dihydrate were purchased from Merck (Darmstadt, Germany). Nonpareil beads (Nu-Pareil® PG, 20/25 mesh, Crompton and Knowles, Mahawah, NJ, USA) of sucrose and starch with mean size of 0.76 mm were used as the core substrate for further coating process. The coating polymers used were HPMC (4 mPa·s, Pharmacoat 904 and 400 mPa·s, Metolose 90-SH, Shin-Etsu Chemical, Tokyo, Japan) and polyacrylic polymer in the form of an aqueous dispersion (Eudragit RS30D, Rohm Pharma, Darmstadt, Germany). Polyethylene glycol (PEG 6000, BASF, Ludwigshafen,

Germany) was used as a plasticizer to coating polymers. All the materials were used as supplied.

Preparation of Multilayer Coated Pellets

The nonpareil beads were coated with three different functional layers in a bottom-spray fluidized bed (Aeromatic, Strea-1, Bubendorf, Switzerland). The coating process was the same as that described previously[9] but the compositions of the coating dispersions were different. The coating level of each layer was expressed as the percentage weight of dry polymer applied with respect to the weight of nonpareil beads used. The inner deposition layer contained 2% (*w*/*w*, based on the weight of nonpareil beads) CM and 3% coating level of HPMC (4 mPa·s). The middle diffusion layer consisted of HPMC (400 mPa·s) of different coating levels (based on the weight of nonpareil beads) and various osmotic agents of varying amounts based on the dry weight of HPMC (400 mPa·s). The osmotic agents used were sodium chloride, glycine, citric acid, and disodium hydrogen phosphate. The outer retention layer comprised Eudragit RS30D at coating level of 7.5% (*w*/*w*, based on the weight of nonpareil beads). Ten percent (*w*/*w*, based on the dry weight of polymer) PEG 6000 was incorporated in each coating layer as a plasticizer.

Viscosity Studies

Apparent viscosities of 2% (*w*/*w*) HPMC (400 mPa·s) solutions containing 5%, 10%, 15%, and 30% of osmotic agents (*w*/*w*, based on the dry weight of HPMC) at 37±1°C were determined using a U-tube of type D in accordance with method I in the British Pharmacopoeia (2001).

Osmolality Measurement

The osmolalities of different osmotic agents at varying concentrations in distilled water were determined by the freezing point method with the aid of an osmometer (Precision System, OSMETTE, Model 5004, Natick, MA, USA). At least three determinations for each concentration were taken and results averaged.

Dissolution Studies

Dissolution tests were performed using a paddle apparatus (USP, Method II, Hanson Research, 72-RL, Chatsworth, CA, USA) at 37±1°C with a rotation speed of 50 rpm as described previously.[9] One gram of coated pellets was accurately weighed and dispersed in 1 L of deaerated distilled water. Five mL of samples were collected at predetermined intervals over a period of 5 h using an automated sampler (Hanson Research, Dissoette 27-6A, Chatsworth, CA, USA). The samples obtained were assayed for CM spectrophotometrically (Hewlett Packard, 8451A, Palo Alto, CA, USA) at 262 nm. Three replicates were carried out and the results averaged. The model-independent time point and mean dissolution time (MDT) approaches were applied for dissolution profiles and dissolution $T_{50\%}$ and MDT values were obtained, respectively. Dissolution $T_{50\%}$ value is defined as the time for 50% of drug released from the pellets and mean dissolution time (MDT) value is defined as the sum of different release fraction periods during dissolution divided by the total amount of drug released. The drug release data were also fitted into a zero-order release kinetic model, and the release rates were calculated from the slope of linear portion of release profiles.

RESULTS AND DISCUSSION

Effect of Sodium Chloride Amount in Diffusion Layer

Five percent, 10%, 15%, and 30% of sodium chloride were incorporated in the diffusion layer at 10% coating level. Figure 1 shows the release profiles

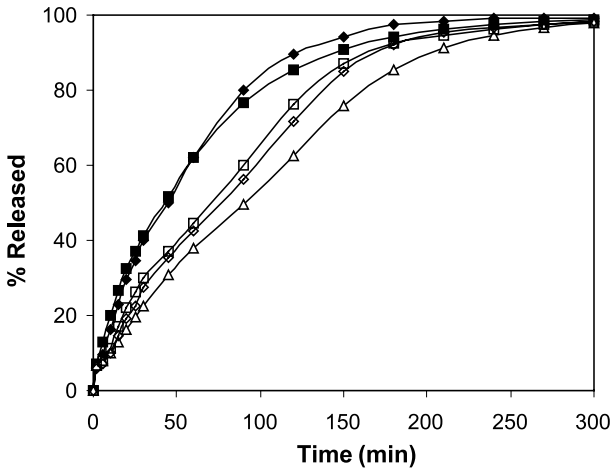

Figure 1. The effects of 0% (◆), 5% (■), 10% (△), 15% (◇), and 30% (□) sodium chloride in diffusion layer on release profiles of pellets coated with deposition layer of 2% CM and 3% HPMC (4 mPa·s), diffusion layer of 10% HPMC (400 mPa·s), and retention layer of 7.5% Eudragit RS30D.

Table 1. Viscosities of HPMC solutions in the presence of various amount of sodium chloride and release parameters for pellets coated with deposition layer of 2% CM and 3% HPMC (4 mpa·s), diffusion layer of 10% HPMC (400 mPa·s) containing sodium chloride, and retention layer of 7.5% Eudragit RS30D.

				Stage I		Stage II	
NaCl (%)	Viscosity (mPa·s)	$T_{50\%}$ (min)	MDT (min)	K_{0-I} (% min^{-1})	R^2	K_{0-II} (% min^{-1})	R^2
0	210.0	44.8	54.9	1.324	0.994	0.772	0.997
5	210.6	43.0	58.5	1.508	0.996	0.727	0.997
10	220.2	90.9	95.6	0.626	0.998	0.436	0.997
15	230.4	77.1	82.2	0.840	0.998	0.461	0.999
30	162.0	65.3	77.3	0.931	0.991	0.511	0.999

of CM from the multilayer coated pellets with different amount of sodium chloride in the diffusion layer. For better understanding of the mechanisms of drug release, the release rates for Stage I (K_{0-I}, <30% released) and Stage II (K_{0-II}, 30–70% released) of the drug release profiles were obtained, respectively. Dissolution $T_{50\%}$, MDT, and viscosity values as well as the release kinetic parameters are listed in Table 1. With increasing amount of sodium chloride in the HPMC solutions, the viscosities slightly increased up to 15% of sodium chloride while 30% of sodium chloride greatly decreased the viscosity of HPMC solution instead. The pellets with 5% sodium chloride showed no significant differences in dissolution $T_{50\%}$ and MDT values compared with those without sodium chloride ($P>0.05$).

Whereas the pellets with 10%, 15%, and 30% of sodium chloride had markedly longer dissolution $T_{50\%}$ and MDT values than pellets without sodium chloride but dissolution $T_{50\%}$ and MDT values of the pellets with 10%, 15% and 30% of sodium chloride decreased with increasing amount of sodium chloride in the diffusion layer ($P<0.05$). The release profiles exhibited multiphase release characteristics with decreased release rates over phase. The first two phases of release profiles were best fitted into a zero-order release model. The release rate in Stage I of dissolution was much larger than that in Stage II of dissolution for each profile. The presence of 10%, 15%, and 30% sodium chloride in the diffusion layer decreased release rates but the retarding effect decreased with the amount of sodium chloride. No retarding effect was observed with 5% of sodium chloride in the diffusion layer with respect to that without sodium chloride in the diffusion layer. These results indicated that existence of sodium chloride in the diffusion layer could delay drug release, but a certain amount of sodium chloride in the diffusion layer was necessary to exert its effect in controlling the drug release.

The water-soluble drug CM in the deposition layer was released through the highly swellable HPMC layer and the less swellable Eudragit layer. At the initial stage of dissolution, sodium chloride dissolved very fast and competed with HPMC for imbibing water, resulting in the delayed relaxation of HPMC and retarded burst release of drug. In addition to its effect on HPMC, sodium chloride also reduced the hydration of Eudragit RS30D.[9] No obvious swelling of pellets was observed during the first few minutes of dissolution.[9] As the drug existed in the inner deposition layer, the relatively less water available in the deposition layer also caused a slower drug release rate. The osmotic pressure of dissolution medium was negligible compared to that in the diffusion layer. With the dissolution of more sodium chloride, the increased osmotic pressure gradient led to increased water influx into the diffusion layer. The latter consequently increased hydration of the HPMC diffusion layer and reduced drug diffusion barrier properties, thus facilitating drug release. The higher water influx and intensive swelling of HPMC gave rise to the expansion of pellet volume and therefore caused longer diffusion path-length for drug release. The erosion of the HPMC diffusion layer was greatly minimized by the presence of the flexible Eudragit retention layer, but the overall effect on drug release was dependent on the overall factors governing drug release. Moderate levels of sodium chloride (10% and 15%) slightly increased the viscosity in the diffusion layer. Conversely, the large amount of sodium chloride in the diffusion layer dehydrated the HPMC molecules and markedly reduced the apparent viscosity of the hydrated HPMC layer in the presence of 30% of sodium chloride owing to the salt-out effect.[10] In this case, the HPMC molecule chains contracted and became less entangled with each other, and the resistance to drug diffusion through aqueous channels composed of hydrated sodium chloride thus decreased, leading to more rapid release of drug. The osmotic pressure difference between the

diffusion layer and the drug-loaded inner deposition layer might impede the drug transport into the outer diffusion layer. However, the drug diffused into the diffusion layer could be pumped out into dissolution medium because of the osmotic pressure gradient across the retention layer. Osmotic driven mechanism was thus involved in the drug release. This osmotic effect was supported by the observation that the drug release was delayed as the osmolality of dissolution medium increased in our preliminary studies. Sodium chloride in the diffusion layer was also released and the osmotic pressure difference gradually decreased. The effect of sodium chloride on drug release diminished with the depletion of sodium chloride after 120 min of dissolution. The net effect of these opposing effects determined the drug release profiles.

Although the release profiles in Stages I and II of drug dissolution from pellets in the presence of sodium chloride at levels of 10%, 15%, and 30% in the diffusion layer apparently fitted well into zero-order model kinetics, the contribution of each release mechanism might change over the course of dissolution. In the multilayer coated pellets in the presence of osmotic agent in the middle diffusion layer, the release mechanisms can be very complex. These included the contribution from drug diffusion through the highly swellable diffusion layer and less swellable retention layer, drug release driven by osmotic pressure difference between the coat and dissolution medium, and drug release caused by potential stretch and erosion of coats. The flexible retention layer maintained the integrity of the coat during dissolution[9] and thus greatly minimized the erosion of the diffusion layer. Hence, the drug release due to coat erosion was negligible. The drug release rate was mainly governed by the diffusion and osmotic contribution, where the release rate governed by osmotic mechanism is related to the osmotic pressure difference across the semipermeable membrane.[4] In Stage I of dissolution, water penetrated into the coated pellets through the Eudragit layer, followed by the fast dissolution of sodium chloride and generation of osmotic pressure inside the coat. The HPMC molecules were not well hydrated for diffusion of drug due to the competition of sodium chloride with HPMC for water. However, the osmotic pressure in the diffusion layer caused more water influx and led to swelling of the HPMC layer. The drug was thus released according to the osmotic pump mechanism. The drug release rate for Stage I of dissolution was principally controlled by the water influx rate and osmotic pressure generated in the diffusion layer. In Stage II of dissolution, it can be expected that HPMC molecules were completely relaxed and the drug diffused out through the viscous HPMC gel layer and hydrophilic quaternary ammonium groups of Eudragit layer. In the meantime, sodium chloride leached out faster than the drug did and nearly all sodium chloride was released after 120 min of dissolution.[9] With the depletion of sodium chloride from the coat and accumulation of sodium chloride in the dissolution medium, the osmotic pressure difference between the diffusion layer and dissolution medium gradually diminished, thus gradually reducing the contribution of osmotic effect to the drug release. This might partially account for the reduced drug release rates in Stage II of dissolution with respect to those in Stage I of dissolution. Over the course of dissolution, both the osmotic pressure and diffusion mechanisms affected the drug release rates but the dominant release mechanism gradually changed from osmotic pressure-controlled to diffusion-controlled. The relative contribution of osmotic pressure effect decreased and diffusion contribution increased. The presence of a certain amount of sodium chloride in the diffusion layer was responsible for the resultant multiphase release profiles and played a predominant role in controlling drug release, particularly in the initial stage of dissolution. The effects of sodium chloride in the diffusion layer on drug release were complicated. It exerted a retarding effect on burst release by competing for imbibed water with HPMC molecules[9] and on the other hand, rendered an enhancing effect by causing more water influx into the diffusion layer and drug release due to osmotic pressure difference. This

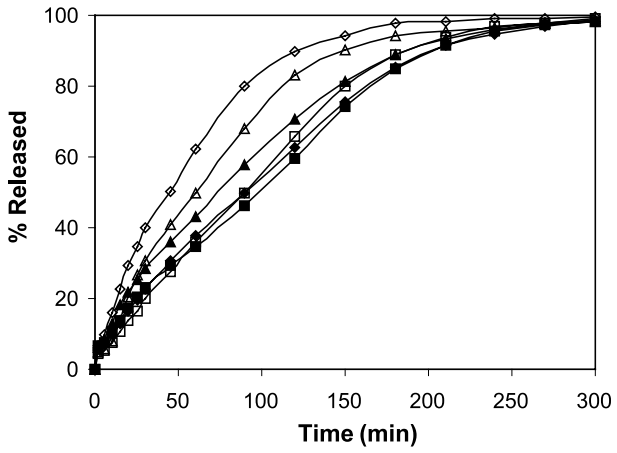

Figure 2. The release profiles of pellets coated with deposition layer of 2% CM and 3% HPMC (4 mPa·s), diffusion layer of 10% (◆, ◇), 15% (■, □), and 20% (▲, △) HPMC (400 mPa·s) with (close symbols) or without (open symbols) 10% of sodium chloride and retention layer of 7.5% Eudragit RS30D.

Table 2. Release parameters for pellets coated with deposition layer of 2% CM and 3% HPMC (4 mPa·s), different coating levels of HPMC (400 mPa·s) diffusion layer with or without 10% of sodium chloride, and 7.5% Eudragit RS30D retention layer.

	Coating level		
	10%	15%	20%
Without sodium chloride			
$T_{50\%}$ (min)	44.8	64.9	60.3
MDT (min)	54.9	94.2	70.0
K_{0-I} (% min^{-1})	1.324	0.563	0.985
K_{0-II} (% min^{-1})	0.772	0.497	0.623
With 10% sodium chloride			
$T_{50\%}$ (min)	90.9	98.4	74.6
MDT (min)	95.6	99.1	83.7
K_{0-I} (% min^{-1})	0.626	0.561	0.832
K_{0-II} (% min^{-1})	0.436	0.412	0.484

osmotic pressure effect was reduced with depletion of sodium chloride into dissolution medium over time. The drug release behavior from the multilayer coating pellets was governed by the above-mentioned release mechanisms.

The coating level of diffusion layer might also influence the sodium chloride effect on drug release. Release profiles of CM from the coated pellets at 10%, 15%, and 20% coating levels of the diffusion layer with 10% sodium chloride and 7.5% coating level of the retention layer are shown in Fig. 2. Release parameters are summarized in Table 2. Addition of the osmotic agent in the diffusion layer increased dissolution $T_{50\%}$ and MDT values compared with those of pellets without an osmotic agent at an equivalent coating level of diffusion layer. The MDT values slightly increased from 95.6 min to 99.1 min as the coating level of the diffusion layer was increased from 10% to 15%. Further increase in the coating level to 20% resulted in a decreased MDT value of 83.7 min. The existence of sodium chloride in the diffusion layer also decreased release rates in Stages I and II of the dissolution profiles at each coating level of the diffusion layer. These further confirmed the retarding effect of the osmotic agent in the diffusion layer on drug release. However, the swelling and erosion of the diffusion layer became noticeable with the increasing coating level of the diffusion layer to 20%. It was reported that pellets with 20% diffusion layer featured more extensive swelling and were more susceptible to coat rupture, leading to erosion of the diffusion layer and faster drug release.[9] The contribution of the erosion of the diffusion layer to drug release mechanism cannot be ignored. The effect of the osmotic agent in the diffusion layer on drug release was thus greatly compromised.

Effect of Osmotic Agent Type

The osmotic pressure can be calculated from the osmotic concentration or osmolality. In general, the osmolality of an osmotic agent is proportional to the number of discrete entities of solute in the solution. Hence, the osmotic pressure of a nonionic osmotic agent is only dependent on the concentration of the solute, while that of an ionic osmotic agent depends on the number of ions in the solution. At the same molal concentration, an ionic osmotic agent exerts a higher osmotic pressure than a nonionic osmotic agent. A preliminary study showed that the presence of HPMC did not affect the solubility and degree of ionization of the osmotic agent in solution. It can be inferred that HPMC in the diffusion layer would not affect the solubility and ionization of the osmotic agents in the coat. Therefore, the osmolalities of osmotic agents in distilled water were measured and correlated with the dissolution $T_{50\%}$ and MDT values of drug released from the pellets containing varying osmotic agents in the diffusion layer as well as release rates in Stage I of the drug dissolution profile.

At 10% (*w*/*w*) of different osmotic agents added in the diffusion layer, the osmolality generated decreased

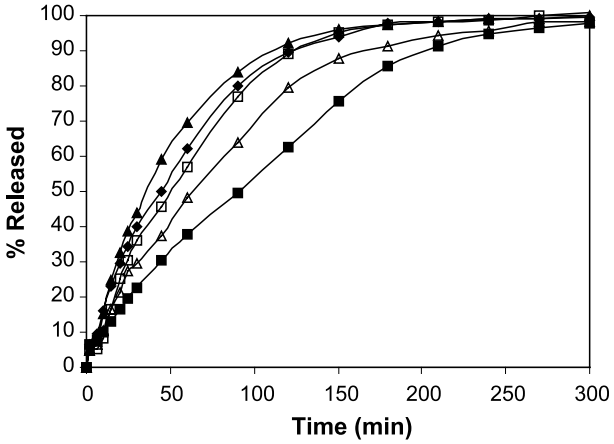

Figure 3. The release profiles of pellets coated with deposition layer of 2% CM and 3% HPMC (4 mPa·s); diffusion layer of 10% HPMC (400 mPa·s) with 10% sodium chloride (■), citric acid (▲), glycine (□), disodium hydrogen phosphate (△), or without osmotic agent (◆); and 7.5% Eudragit RS30D retention layer.

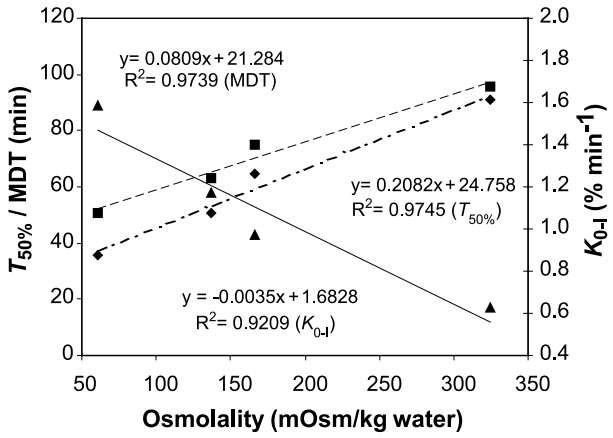

Figure 4. The relationships between osmolalities of osmotic agents and dissolution $T_{50\%}$ (◆), MDT (■), as well as K_{0-I} (▲), respectively, for pellets coated with deposition layer of 2% CM and 3% HPMC (4 mPa·s), diffusion layer of 10% HPMC (400 mPa·s) and 10% of various osmotic agents, and 7.5% Eudragit RS30D retention layer.

in the following order: sodium chloride>disodium hydrogen phosphate>glycine>citric acid. Release profiles are illustrated in Fig. 3. As shown in Fig. 4, dissolution $T_{50\%}$ and MDT values increased with increasing osmolality of the osmotic agents. This indicated that the osmotic effect in the diffusion layer retarded drug release and its effect was related to the osmolality of osmotic agent and thus, the osmotic pressure in the diffusion layer. Interestingly, the release rate in Stage I of dissolution was inversely proportional to osmolality of the osmotic agents, while the release rate in Stage II of dissolution was not correlated to osmolality. These further confirmed the dominant effect of osmotic agents on drug release rate in the initial phase of dissolution. However, the dissolution $T_{50\%}$ and MDT values of 35.8 and 50.5 min for pellets with citric acid in the diffusion layer were less than those for pellets without citric acid, 44.8 and 54.9 min, respectively. This was attributed to the interaction of citric acid with the Eudragit polymer. Citric acid is an organic acid with a pK_a value of 3.13 and has been reported to affect the permeability of Eudragit RS coats.[11] The dissociated form of the organic acid molecules was able to interact with cationic quaternary ammonium groups in Eudragit RS30D molecules by an ion-exchange mechanism and enhanced the permeability of Eudragit RS30D coat. An undissociated form of the organic acid molecules could penetrate into the hydrophobic segment of Eudragit RS molecules and act as a plasticizer. The synergistic effects caused increased hydration and permeability of Eudragit RS film. Therefore, the osmotic effect on drug release from the multilayer pellets was not clearly observed since osmotic pump effect only occurred when the diffusion barrier remained as a semipermeable membrane.[12] This explains the higher release rate of coated pellets when citric acid was included as an osmotic agent.

CONCLUSIONS

Addition of an osmotic agent in the diffusion layer was able to modify the drug release profile, but its effect also depended on the amount and type of osmotic agent in the diffusion layer as well as the coating level of diffusion layer. A certain amount of osmotic agent in the diffusion layer was necessary to exert its effect on retarding drug release due to competition for imbibed water with HPMC molecules, but a large amount of osmotic agent in the diffusion layer caused the decreased viscosity of the diffusion layer, thus compromising the retarding effect on drug release. The osmotic agent effect played a dominant role in controlling drug release, particularly in the initial stage of dissolution. With depletion of the osmotic agent, its effect on drug release was also reduced. At a higher coating level of the diffusion layer, the retarding effect of the osmotic agent was hindered owing to the extensive swelling and erosion of the diffusion layer. The net effect of these opposing effects determined the performance of drug release. Diffusion and the osmotic pressure effect mainly contributed to the release mechanisms. However, it must be noted that the drug release behavior from the multilayer coated pellets can be rather complex, and the release mechanisms included were much more than simple diffusion and osmotic pump effect. Some phenomena, such as induction of osmotic pressure in the sugar core, rupture and re-sealing of the retention coat, and possible dissolution or erosion of HPMC layer due to rupture at higher coating levels of diffusion layer, were also observed in the dissolution and increased the complexity of release mechanisms.

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