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Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes

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Abstract

Complex formation between drugs and ion-exchange resins was investigated and the effects of coating by various aqueous polymeric dispersions on the complexes were evaluated for developing new sustained-release fast-disintegrating tablets (FDTs). Complexes of ion-exchange resin and dextromethorphan, a model drug, were prepared using different particle sizes of the resins. Aqueous colloidal dispersions of ethylcellulose (EC) and poly(vinyl acetate) (Kollicoat® SR30D) were used for fluid-bed coating. Based on drug loading, release profiles, and scanning electron microscopy (SEM) images, the coated particles were granulated with suitable tablet excipients and then compressed into the tablets. Drug release profiles and SEM pictures were compared before and after the manufacturing processes. As the particle size of resins increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. Higher coating level decreased the release rate further. In contrast to EC, Kollicoat® SR30D coated particles could be compressed into tablets without any rupture or cracks on the coating since the mechanical properties of the polymer was more resistant to the manufacturing processes. This resulted in no significant changes in release rates. SEM showed the mechanical strength of the polymers affected the morphological change after compression. When the drug release profiles were applied into *Boyd model* and *Higuchi equation*, the linear relationship was observed, indicating that the diffusion within the resin matrix is the rate-controlling step.

Keywords: Ion-exchange resin; Fast-disintegrating tablet; Polyvinyl acetate; Ethylcellulose; Fluid-bed coating; Diffusion; Sustained release

1. Introduction

Since the initial success of the fast-disintegrating tablet (FDT) technologies, they have been steadily improving for development of more patient-friendly dosage forms (Dobetti, 2001; Fu et al., 2004; Sastry et al., 2000). The FDT system has advantages of solid dosage forms, such as good stability, accurate dosing, small packaging size, and easy handling, as well as those of liquid formulations, such as easy administration and minimal risk of suffocation. Therefore, it is beneficial for children, elderly, and schizophrenic patients who have difficulty in swallowing conventional solid dosage forms (Dobetti, 2001; Seager, 1998). Moreover, it has been extending to more general patients requiring daily medication regimens.

Upon introduction into the mouth, FDTs start to dissolve or disintegrate immediately on the tongue even in the absence of external water for easy administration of active pharmaceutical ingredients (APIs). After a tablet disintegrates or dissolves, the active ingredient in the tablet remains in the oral cavity until it is swallowed. Upon swallowing, the active ingredient can be absorbed from the gastrointestinal tract resulting in the desired therapeutic effect. After swallowing, there should be minimal or no residue in the mouth. Those APIs that have bad tastes or are instable in the gastric environment can be coated with polymer layer for taste masking and increasing the stability in the stomach.

Despite successes of FDT formulations, there are currently no formulations that can deliver an API in a sustained manner, e.g., delivery for 12 h. FDT formulations with sustained release properties would bring new benefits that were not possible before. One of the controlled release mechanisms is ion-exchange controlled drug delivery. The active ingredients, if they are ionized, can be complexed with counter ions of ion-exchange

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resins (Kim, 2000; Motycka and Nairn, 1978; Motycka and Nairn, 1979; Motycka et al., 1985; Raghunathan et al., 1981). The advantages of utilizing ion-exchange resins include simple preparation method, and no uncontrolled burst effect in the drug/resin complex even at high drug loading. The only limiting factor for drug loading is the limited exchanging capacity of the resin (Kim, 2000). When active ingredient/resin complexes are administered orally, the active ingredient can be released by the ion-exchange reaction with counter ions present in the GI tract (Kim, 2000). The ion-exchange resin complexes are often coated with a polymer layer for better control of drug release (Ichikawa et al., 2001; Motycka et al., 1985; Pongjanyakul et al., 2005; Raghunathan et al., 1981). The drug release rate can be controlled by one or a combination of diffusion resistance of the core (resin complex), diffusion resistance of the coating, and ion-exchange reaction rate, depending on the properties of the ion-exchange resins and applied coating materials (Jeong et al., 2007).

Most of the previous applications using bare or polymer-coated drug/resin complexes have been focused on suspension dosage forms. When resin complexes are applied in the FDT formulations, the advantages of both the resin and the tablet dosage form can be exploited. Acceptable tablets containing drug/resin particles should have sufficient physical integrity to withstand handling and also disintegrate rapidly into individual particles on the tongue. The size of the disintegrated particles should be small, preferably less than 300 μm to avoid any sandy feeling in the mouth. The polymer-coated resin particles should not fuse into each other during compaction. Moreover, the drug release rate should not be changed significantly by the compaction process. They may deform but should not rupture in order to keep the initial release rate (Dashevsky et al., 2004). Recently, we developed a new technology based on highly plastic granules for making FDTs (Fu et al., 2005; Jeong et al., 2005). The technology utilizes the conventional wet granulation process and tablet press for cost-effective production of tablets. The objective of this study was to develop FDT formulations for sustained release properties based on the ion-exchange mechanism.

2. Materials and methods

2.1. Materials

An ion-exchange resin (Amberlite® IRP69, polystyrene sulfonate, Na^+ form, crosslinkage of 8%) was purchased from the Sigma–Aldrich Co. (St. Louis, MO) and its cation exchange capacity is ~5 mequiv./g. It was purified by rinsing 200 g of wet resin three times with 1000 mL of distilled water, twice with 95% ethanol, and then twice with 1000 mL of distilled water to remove the ethanol. Each treatment took at least 8 h by a batch process. After filtration, the resin was dried in a 45 °C oven. Dextromethorphan hydrobromide monohydrate (DM), a model drug, was obtained from Spectrum® (Spectrum Chemical Mfg. Corp., New Brunswick, NJ). Ethylcellulose (EC) aqueous dispersions including Aquacoat® ECD and Surelease® were generously donated by FMC BioPolymer (Newark, DE) and Colorcon (West Point, PA), respectively. Kollicoat SR® 30D (polyvinyl acetate aqueous dispersion) was kindly donated by BASF (BASF Corp., Mont Olive, NJ). Mannogem™ EZ Spray, spray-dried mannitol from SPI Pharma Inc. (New Castle, DE), was used as the major tablet excipient.

2.2. Preparation of DM-loaded resin complexes

The DM/Amberlite® IRP69 complexes were prepared by a single batch process. The purified ion-exchange resin particles were sieved using a Rotap RX-29 (Mentor, OH) to divide the particles into 106–150 μm, 75–106 μm, and <38 μm. Each set of particles was dispersed in a 1.9% (w/v) drug solution with a net weight ratio of 1:1 under magnetic stirring at room temperature for 24 h. To determine the equilibrium rate, a small amount of supernatant was collected at predetermined time intervals to monitor the changes of the DM concentration in the solution. The collected samples were filtered and diluted before injection into an HPLC. The complex was separated by filtration.

2.3. Preparation of polymer-coated resin complexes

The DM-loaded resin complexes were coated in a fluidized bed coater, MFL-01 (Vector Corporation, Marion, IA) to obtain predetermined weight gain. A bottom spray coating method (Wurster process) was applied for this process. The dried resin complex (40 g) was mixed with micronized talc (0.8 g) to improve the initial flowability before the coating process. The coating solution was diluted to 10.0% (w/w) solids content. In order to enhance film formation and flexibility, a plasticizer (triethyl citrate) was added. Formulations of the coating solution and the operating conditions of the fluid bed coater are shown in Table 1. The percentage coating was defined as the amount of coating applied compared to the amount of core (resin complex).

Table 1
Formulations and operating conditions of the fluid bed coater for preparation of coated resin particles

Conditions	Aquacoat® ECD	Surelease®	Kollicoat SR® 30D
Operating conditions			
Inlet air flow (L/m)	45.0	43.0	42.0
Inlet air temperature (°C)	80.0	80.0	60.0
Exhaust temperature (°C)	27.5	26.7	24.3
Nozzle pressure (psi)	15.8	15.6	15.7
Pump speed (rpm)	9.0	10.0	10.0
Formulation			
Aquacoat® ECD (g)	24.23	–	–
Surelease® (g)	–	40.0	–
Kollicoat SR® 30D	–	–	31.75
HPMC (g)	0.93	–	–
Triethyl citrate (g)	1.80	–	0.47
Water (g)	73.04	60.0	67.78

2.4. Granulation and compression procedures

A high shear granulation method was applied to prepare the granules containing coated resin particles. The general processing step for the granulation is similar to the one described previously (Fu et al., 2005; Jeong et al., 2005), and the only difference was adding an API in the coated resin particles. The amount of DM in each formulation was adjusted to 60 mg and Mannogem™ EZ Spray was compromised with the coated particles. Mannogem™ EZ Spray, fructose (5%), coated particles, cherry flavoring (0.3%), citric acid (0.5%), and aspartame (2%) were weighed, placed into a granulation bowl, and then dry-mixed for 1 min with a mixer speed of 400 rpm and chopper speed of 300 rpm. 50% sucrose in EtOH solution was transferred and mixed for another 30 s. The wet mass was sieved using a Fitz-Sieve with a 4 mm round-hole sieve screen, a 1.5 mm clearance, and a 500 rpm sieve speed.

The collected wet granules were spread evenly on trays and then placed on drying racks in a drying room set at 27 °C and 30% RH. If the moisture content of the granules was 1.6–1.9%, then proceeded to sieving. The collected granules were stored in a plastic bag. A lubricant (magnesium stearate) was blended before compression. The blend time and speed were 15 min and 25 rpm, respectively. 500 mg tablets were compressed on a single punch Carver Laboratory Press (Carver Inc., Wabash, IN) at different compression pressures using plane-face punches with 0.5-in. diameters.

2.5. Drug release test

Drug release tests were conducted according to USP 27 Apparatus 2 guidelines (paddle method) (Vankel® VK 7000, Vankel, Edison, NJ) with 900 mL dissolution medium maintained at 37 ± 0.5 °C and mixed at 100 rpm. The dissolution media used in this study were 0.1 N HCl (pH 1.1–1.2). Samples were withdrawn at predetermined time intervals and analyzed for drug content using an HPLC system (Agilent 1100 Series, Agilent Technologies, Waldbronn, Germany) at a wavelength of 280 nm. Samples were filtered with 0.2 μm nylon filters, and then 20 μL of the sample was injected. The column used was a Symmetry® C_{18} 5 μm (3.9 mm × 150 mm) (Waters Corp., Milford, MA) with a Sentry™ guard column (Symmetry® C_{18} 5 μm, 3.9 mm × 20 mm). The mobile phase contained a mixture of aqueous buffer (10 mM KH_2PO_4 adjusted to pH 2.6 with phosphoric acid) and acetonitrile in a volume ratio of 26:74. The retention time of DM was 3.1 min.

2.6. Scanning electron microscopy (SEM)

The morphologies of resin particles and tablets were examined using SEM. Dried samples were attached to specimen stubs using double-sided copper tape and sputter coated with gold-palladium in the presence of argon gas using a Hummer I sputter coater (Anatech Ltd., Denver, NC). The samples were imaged with a JEOL JSM-840 scanning electron microscope (JEOL USA Inc., Peabody, MA) using a 5 kV accelerating voltage, 26–28 mm working distance, and a probe current of 3×10^{-11} amps.

2.7. Drug release kinetics

In the present study, two commonly used mathematical relationships (Boyd and Higuchi) were employed to understand the drug release kinetics from the coated resin particles (Boyd et al., 1947; Higuchi, 1961). As already suggested in the Boyd model (Boyd et al., 1947; Reichenberg, 1953), drug release from a resin complex can be controlled by two well-known mechanisms. One is the diffusion of drug across the thin liquid film at the surroundings of the resin particle and the other is the diffusion of freed drug in the matrix. Since these diffusion mechanisms are sequential steps, the slower one would be rate-limiting. Assuming that the diffusion of a drug in the matrix is the rate-limiting step, and all the resin particles are uniform spheres (radius r), the fraction of drug released, F, is given by the following expression (Boyd et al., 1947):

$$F = \frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{e^{-n^2 Bt}}{n^2} \quad \text{where} \quad B = \frac{\pi^2 D_i}{r^2} \tag{1}$$

M_t and M_∞ are the amounts of drug released after time t and after infinite time, respectively. B is the rate constant, D_i represents the effective diffusion coefficient of the exchanging ions inside the resin particle, and n is the summation variable. For F values higher than 0.85, a first term approximation can be used and the equation is reduced to (Reichenberg, 1953):

$$F = 1 - \frac{6}{\pi^2}e^{-Bt} \quad \text{or} \quad Bt = -\log_e\frac{\pi^2}{6}(1-F)$$
$$= -2.30258\log_{10}(1-F) - 0.49770 \tag{2}$$

If the F value is lower than 0.85, the equation becomes:

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi\left(1 - \frac{\pi F}{3}\right)^{1/2}$$
$$= 6.28318 - 3.2899F - 6.28318(1 - 1.0470F)^{1/2} \tag{3}$$

At a value of $F = 0.85$, Eqs. (2) and (3) gave values of Bt agreeing to within 0.005, corresponding to a variation in F of less than 0.001 (Reichenberg, 1953). If the plot Bt corresponding to the F value against time gives a straight line, it can be assumed that drug diffusion within the resin matrix is the rate-limiting step (Atyabi et al., 1996; Ichikawa et al., 2001; Motycka and Nairn, 1978; Motycka and Nairn, 1979).

One of the most famous and widely used mathematical equations to describe the drug release rate from matrix systems is the Higuchi equation (Higuchi, 1961). It is still often applied to analyze the experimental data to get a rough idea of the underlying release mechanisms (Siepmann and Peppas, 2001). According to the equation, the cumulative amount of drug released (M) can

be described by the following equation:

$$\frac{dM}{dt} = \frac{1}{2}\left[\frac{D(2A - C_s)C_s}{t}\right]^{1/2} \quad (4)$$

where M is the amount of drug released after time t, and D is the diffusion coefficient of the drug. A and C_s are the total amount of drug in a unit volume of matrix and the solubility of drug in the polymer matrix, respectively. Eq. (4) can be expressed by Siepmann and Peppas (2001):

$$\frac{M_t}{M_\infty} = Kt^{1/2} \quad (5)$$

where M_∞ is the amount of drug released after infinite time, and K is a constant. Therefore, the fraction of drug released is proportional to the square root of time. In this case, diffusion will be the major drug release mechanism, and the above relationship can be regarded as an indicator for diffusion-controlled drug release.

3. Results and discussion

3.1. Effects of particle size on the equilibrium rate and release profiles

Based on the *Boyd model*, the drug release from a resin complex can be controlled by either the diffusion of drug across the thin liquid film at the surrounding of the resin particle or the diffusion of freed drug in the matrix. The former one is usually recognized as the rate-limiting step in dilute solutions, whereas the latter one is rate-limiting in more concentrated solutions. The particle size of an ion-exchange resin affects both diffusion phenomena. A fine mesh particle can have more surface area for diffusion and also contain less internal volume through which ionic drugs or counter ions can diffuse. Therefore, decrease in particle size will reduce the time required to reach equilibrium, and this can be easily confirmed by the Fig. 1(A).

When the particle size was less than 38 μm, equilibrium was reached within 3 h (Fig. 1(A)). However, bigger particles required longer time; for example, it took 30 h for the particles 75–106 μm in size to reach equilibrium and more than 50 h for the particles 106–150 μm in size. Regardless of the particle size, the drug loading approached almost the same point. Drug loading efficiency might be more dependent on the functional groups, ionic forms, and crosslinking ratio of the resin rather than on the particle size.

When the reaction time is long enough, most of the functional groups can be loaded with ionic drugs. The ion-exchange reaction is reversible, so drug release from the loaded resin complex would be the reverse way of the drug loading. As shown in Fig. 1(B), as the particle size decreased, the drug release rate increased due to the increased surface area of the resin complexes. Therefore, particle size variation is one way to modify the release rate.

Ion-exchange is a reaction between the functional groups inside resin particles and the ionic molecules in the surrounding medium. The equilibrium rates are different depending on various factors. Crosslinking ratio had a strong influence on the equilibrium rate (data not shown). When an ion-exchange resin is highly crosslinked, it is quite resistant to the diffusion of various ions and ionic drugs through it. Therefore, the time required to reach equilibrium will take much longer.

The equilibrium rate will affect drug loading efficiency and processing time. If the ion-exchange reaction finishes before equilibrium is reached, the drug loading efficiency decreases, resulting in an increased ratio between the amount of processed drug particles and that of tablet excipients. Bigger tablets may not be considered a patient-friendly dosage form and also make disintegration time longer.

As shown in Fig. 2, the DM release profiles were applied into the *Boyd model* and found to give linear *Bt–t* plots, which means that drug diffusion in the matrix may be the rate-limiting step, even though the slopes were strongly dependent on the particle size of the ion-exchange resins. In the case of the very fine resin particles, less than 38 μm, it was hard to obtain a linear region after a certain point using the obtained data. Since the F value is higher than 0.85 within 30 min,

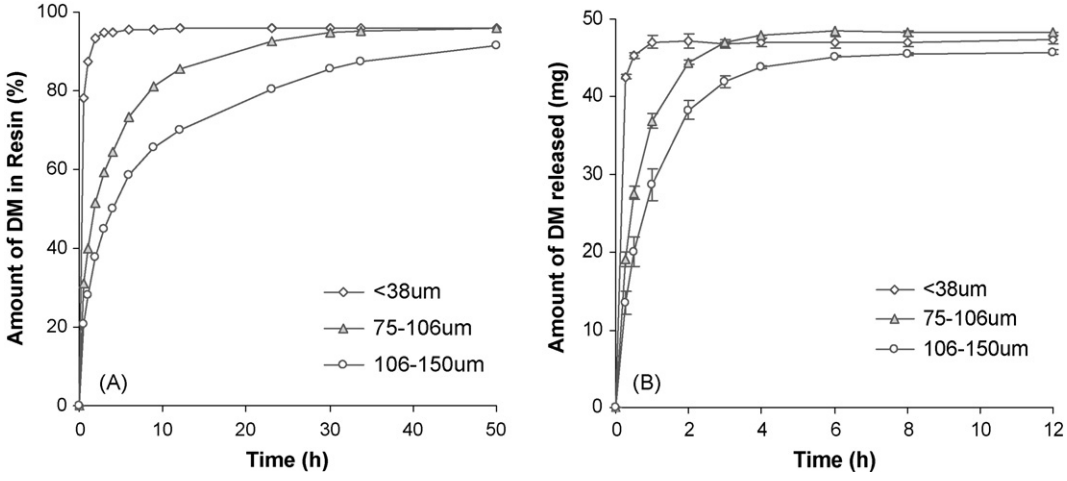

Fig. 1. Equilibrium rates of DM loading into Amberlite® cation-exchange resins with three different particle sizes (A) and *in vitro* release of DM from the DM-loaded ion-exchange resin complexes in 0.1 N HCl at 37 °C.

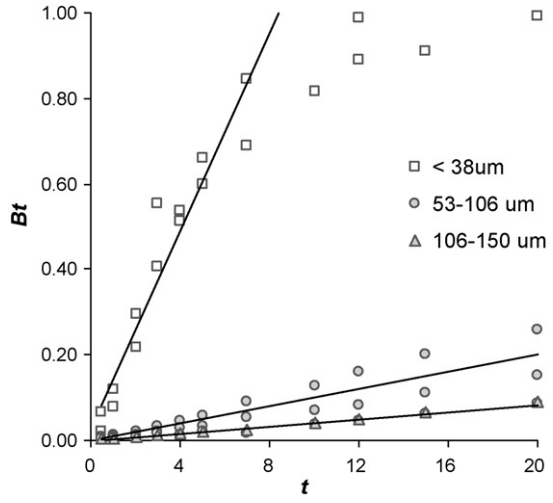

Fig. 2. Plots of *Bt* vs. *t* for uncoated DM-loaded Amberlite® complexes with different particle sizes using the release data in Fig. 1(B).

this shows that most of the bound drug was released very quickly.

3.2. Effect of different polymer coating levels

The amount of DM loaded into 100 mg of resin complex was found to be 48.94 ± 1.70 mg. The DM release profiles of the Aquacoat®, Surelease®, and Kollicoat® SR 30D coated resin particles are shown in Fig. 3. The percentage level of coating was defined as the weight gain relative to the amount of core, and 12-h release profiles were investigated at coating levels from 0 to 30%. Without coating, drug release was very fast. However, as the coating level increased, the release rate decreased. Since the drug release rate is strongly dependent on the coating level, the release rate could be modified easily by changing the coating level. Increasing the coating thickness by applying greater amount of the polymer dispersion is a way to reduce the release rate.

Usually, water-soluble components are added to the EC coating solution to modify the drug release kinetics. They can include sugars, salts, surfactants, and hydrophilic polymers (HPMC, cellulose ether). During dissolution, they can leach out of the coating membrane resulting in a more permeable coating, thus

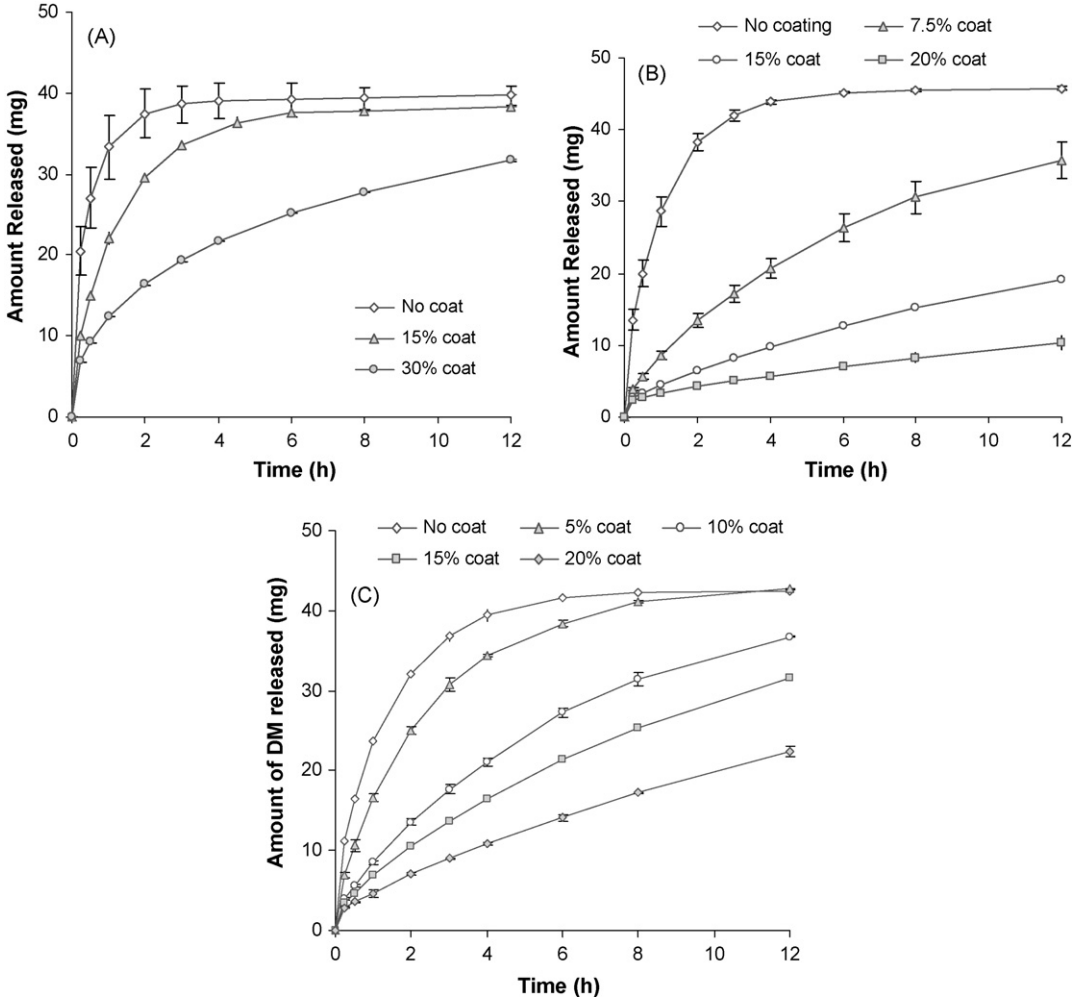

Fig. 3. *In vitro* release of DM from different levels of Aquacoat® (A), Surelease® (B), and Kollicoat® SR 30D (C) coatings on drug-loaded Amberlite® IRP 69 resin particles in 0.1 N HCl (pH 1.2) at 37 °C. A 15% coat indicates that the amount of coating is 15.0% (w/w) relative to the amount of core (drug/resin complex).

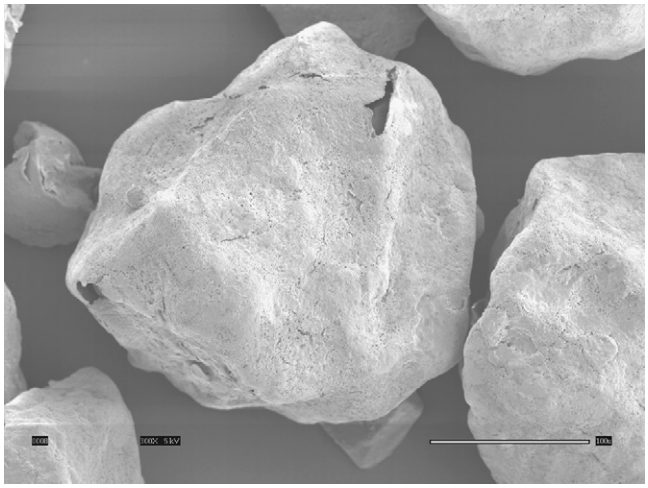

Fig. 4. Scanning electron micrographs of Aquacoat®-coated DM/Amberlite® IRP 69 resin complexes after dissolution testing.

accelerating drug release (Bodmeier et al., 1997). In this study, triethyl citrate and HPMC were incorporated into the Aquacoat® coating solution. These excipients can be leached out of the membrane during dissolution testing (Fig. 4) (Porter, 1997). However, no extrinsic plasticizers and release rate modifiers were added to the Surelease® coating solution, and the release profiles were generated only from different coating levels based on the amount of applied Surelease® components. Surelease® is known to be manufactured through hot melt extrusion and a plasticizer is added during the early stages of the process. During the process, ammonium oleate is formed *in situ* to stabilize and form the dispersion of plasticized EC particles (Porter, 1997).

Kollicoat® SR 30D is comprised of a poly(vinyl acetate) aqueous dispersion stabilized with povidone and sodium lauryl sulfate. The minimum film forming temperature of this polymer (pure dispersion) is 18 °C, which can be lowered by using plasticizers (Dashevsky et al., 2005). Even though the dispersion can be used without any plasticizers, the plasticizers can improve film formation and flexibility. With low amount of triethyl citrate (10%), more than 137% elongation was achieved without any change in drug release profiles (Dashevsky et al., 2004). When the films of this polymer did not include plasticizers, they were a little brittle in the dry state. However, when the films were wet, they were flexible enough to be elongated due to the plasticizing effect of water.

Fig. 5 shows the SEM pictures of uncoated (A), Aquacoat® (B), Surelease® (C), and Kollicoat® SR 30D (D) coated resin particles (20% coating level). As shown in the figures, the coating is consistent with good surface integrity. However, the morphology of Kollicoat® SR 30D coated resin particles looks better than the others.

When examined the SEM pictures of Kollicoat® SR 30D-coated resin particles before and after release test, the integrity of the coating remained constant and crack-free even after release test, offering good mechanical strength to the film (data not shown). Moreover, no pores in the coating films were observed. Therefore, it can be assumed that the diffusion properties of the films are constant during the release test.

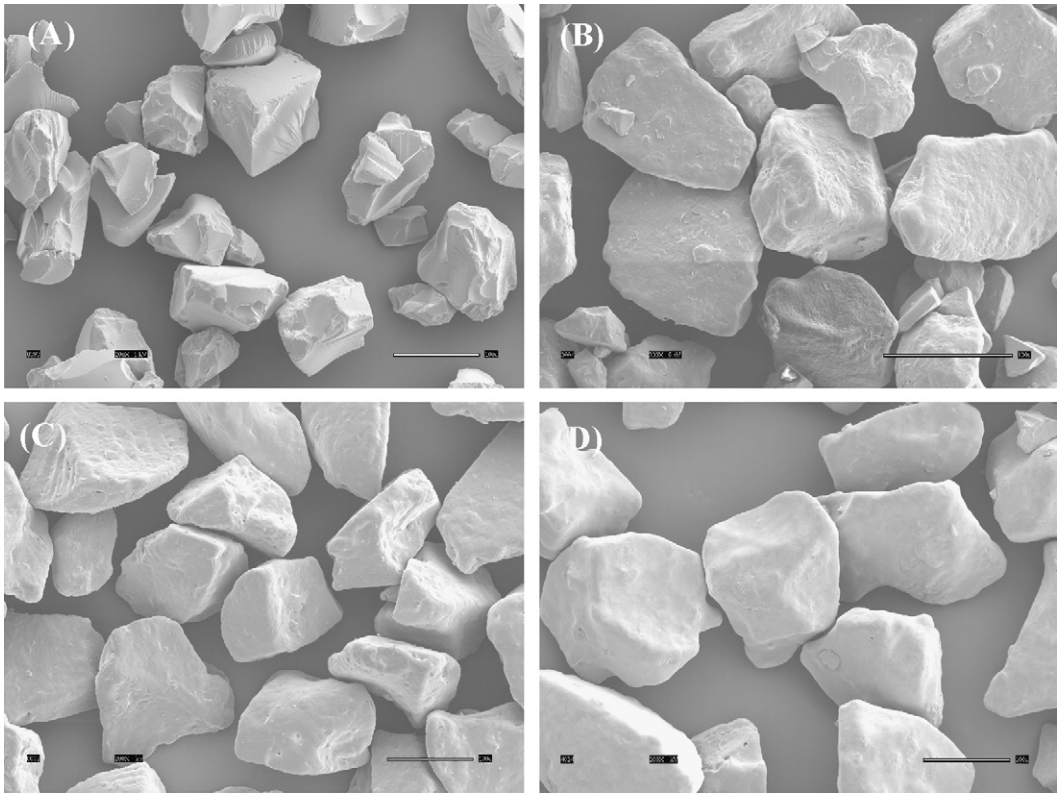

Fig. 5. Scanning electron micrographs of uncoated (A), Aquacoat® (B), Surelease® (C), and Kollicoat® SR 30D (D)-coated DM/Amberlite® IRP 69 resin particles (20% coating level).

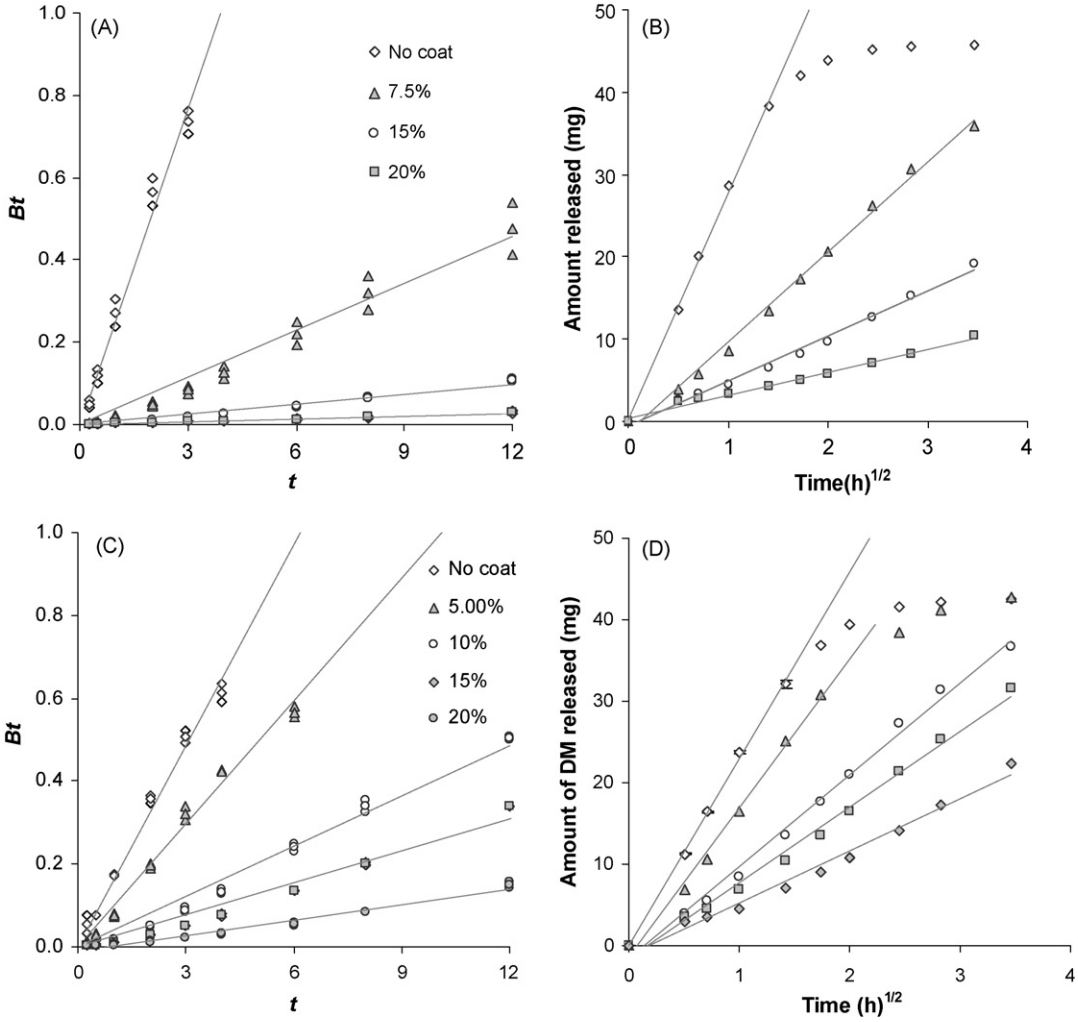

Fig. 6. Plots of *Bt* vs. *t* (left, A and C) and DM release following the *Higuchi equation* (right, B and D) for Surelease® (top) and Kollicoat® SR 30D-coated (bottom) resin particles.

It was previously shown that when the *Boyd model* used, the release rates from the uncoated resin particles yielded a linear *Bt–t* relationship, indicating that drug diffusion in the resin matrix is the rate-limiting step (Pongjanyakul et al., 2005). However, this explanation may not be used for the polymer-coated resin particles because it is not reasonable to assume that the resin complex core and polymer coating are homogeneous systems. We already investigated the exact release kinetics of polymer-coated drug/ion-exchange resin complexes for sustained drug delivery using a new mathematical modeling (Jeong et al., 2007). A comprehensive mathematical model using a mechanistic approach showed that the rate-limiting factor of the uncoated resin particles was diffusion through the core matrix. Moreover, in the coated particles the rate-limiting step was diffusion through the coating membrane. However, *Boyd model* is still simple and fast to understand the diffusion properties using the *Bt–t* relationship regardless of coating.

As shown in Fig. 6(A) and (C), when the DM release profiles were applied into the *Boyd model*, they yielded linear *Bt–t* plots, suggesting that drug diffusion within the matrix is the rate-controlling step, even though the slopes of the plots were strongly dependent on the coating level. Therefore, increasing the coating thickness by applying a greater amount of polymer dispersion is one way to reduce the diffusion rate through the coating. Again, one of the limitations of this model is that the ion-exchange resin and coating were treated as homogeneous systems and coating was just incorporated into the resin matrix. Moreover, the assumption of the model is that the rate-controlling step is either the diffusion of drug across the thin liquid film at the surrounding of the resin particle or the diffusion of freed drug in the matrix; the coating was not considered here.

On the other hand, even though the Higuchi equation suffers from a number of approximations, it is still a useful method to examine drug release data and to obtain drug release rates (Siepmann and Peppas, 2001). If drug release is based on a diffusion mechanism, the plot of M as a function of $t^{1/2}$ will result in a linear relationship. Plots of the fraction of DM released as a function of $t^{1/2}$ showed linearity fitting as shown in Fig. 6(B) and (D). This rough and simple analysis of the release data is consistent with the fact that diffusion is the rate-limiting step in the release mechanism.

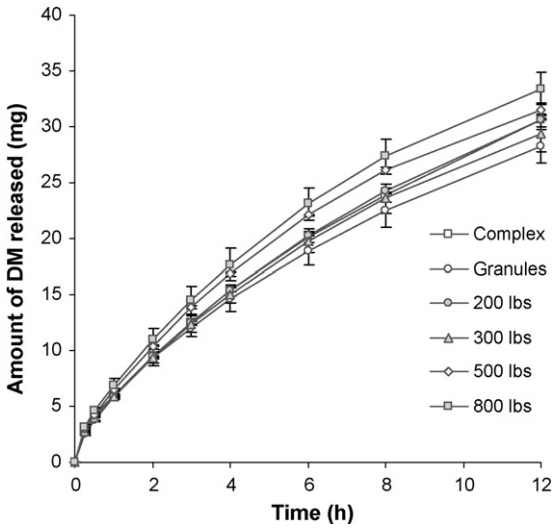

Fig. 7. Influence of granulation and different compression pressures on drug release profiles from Kollicoat® SR 30D-coated DM/Amberlite® IRP 69 resin particles. Granules and tablets contain the coated resin particles with the same amount of drug.

3.3. Effect of granulation and compression procedures

In case of EC aqueous dispersions, granulation and compression processes affected drug release rate significantly (data not shown). Both processes caused film damage, resulting in a significant change in the drug release rate. However, for Kollicoat® SR 30D-coated resin particles, there were almost no changes in the drug release profiles before and after the granulation process (Fig. 7). Moreover, the effect of different compression pressures up to 300 lbs was minimal due to the good mechanical properties of the polymer films. When the compression pressure was higher than 500 lbs, the drug release rate increased slightly, but there was no significant difference.

Fig. 8 shows the SEM pictures of the various polymer-coated DM/ion-exchange resin particles in tablets after dissolution test. In case of Aquacoat® and Surelease® coating, after granulation and compression, the coating film did not keep good surface integrity compared to the coated particles. Since the mechanical strength of the EC coating was not good enough, the EC film was sensitive to compression. As a result, the surface of the coating gave crack or even rupture and this might have caused the increased release rates. Moreover, the coating of some particles showed some peeling (Fig. 8(B)), indicating that it is not very resistant to compression forces. The mechanical strength of the EC coating has been considered not as strong as coatings with acrylic or vinyl polymers. Therefore, when the coated resin particles were compressed, the surface of the coating was expected to be rough and discontinuous, leading to an increased release rate.

However, in case of Kollicoat® SR 30D-coated resin particles, no cracks were observed (Fig. 8(C)), suggesting that the coating had better mechanical properties. The small increase in drug release may not necessarily be attributed to film rupturing or crack formation, but rather, to a thin-

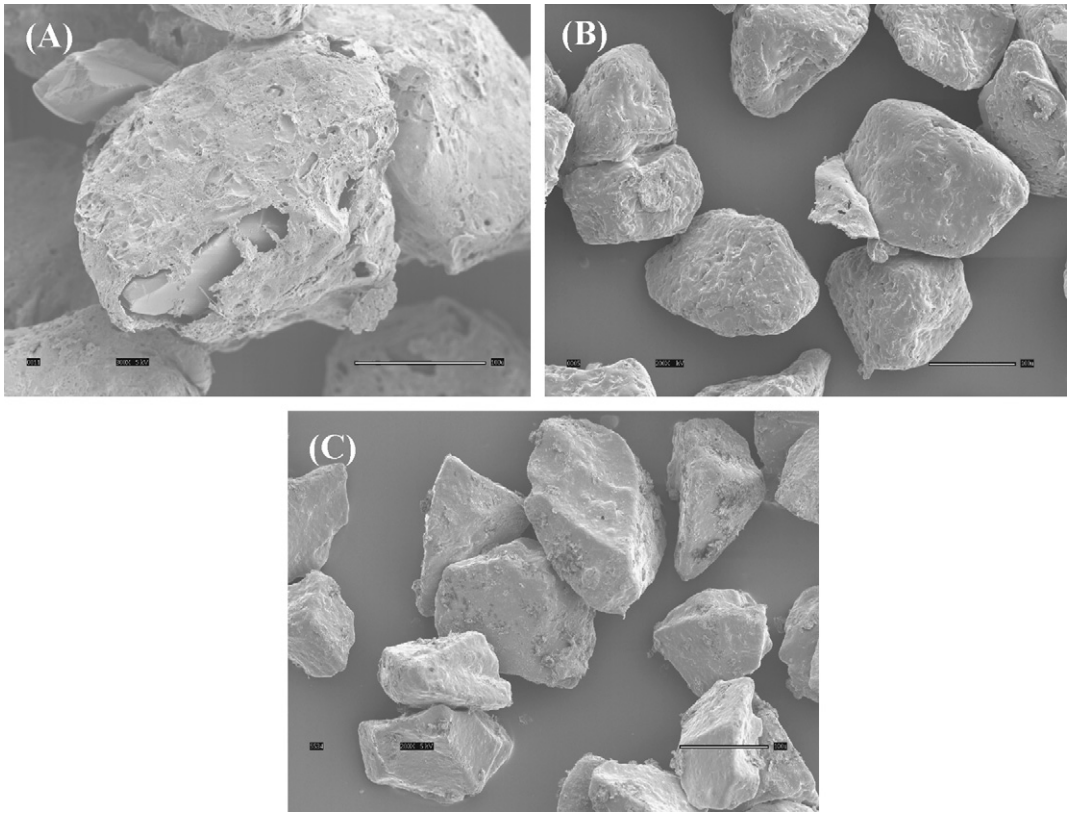

Fig. 8. Scanning electron micrographs of Aquacoat® (A), Surelease® (B), and Kollicoat® SR 30D (C)-coated DM/Amberlite® IRP 69 resin particles from compressed tablets after release testing.

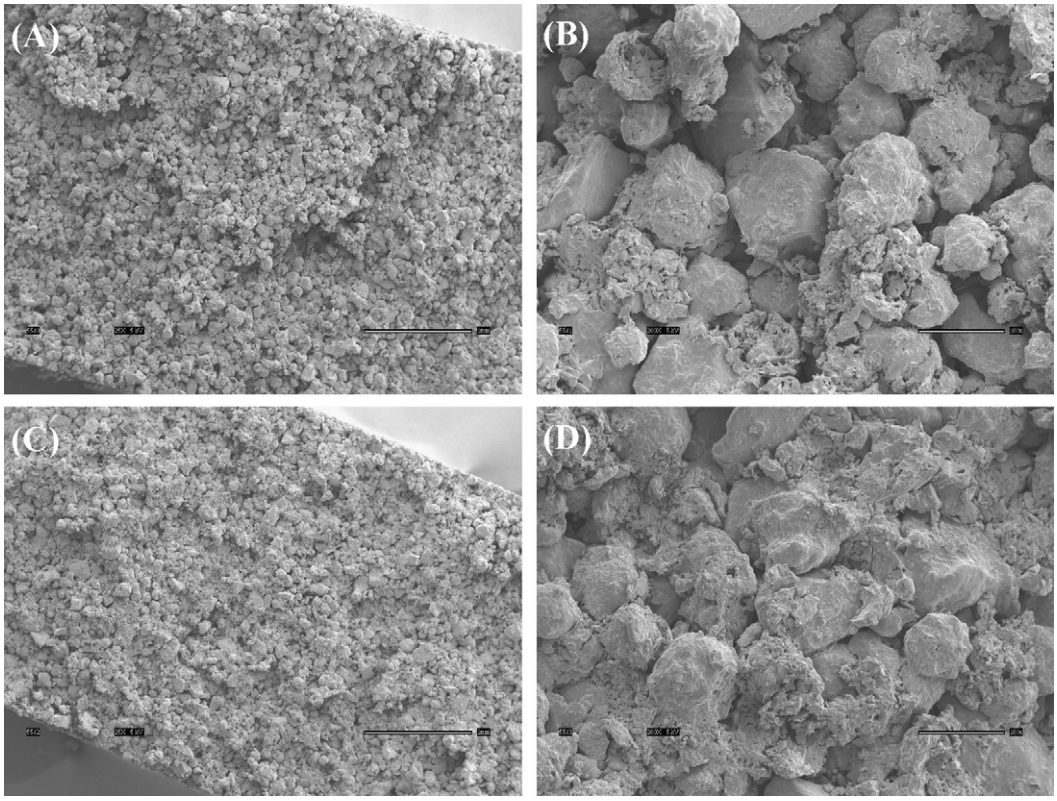

Fig. 9. Scanning electron micrographs of Kollicoat® SR 30D-coated DM/Amberlite® IRP 69 resin particles from compressed tablets with two different magnifications (25× and 200×). The compression pressures used to make the tablets were 200 lbs (A and B) and 300 lbs (C and D).

ning of the flexible film brought about by the compression pressure.

Fig. 9 shows the inner structures of the tablets prepared using the formulation described in the granulation method. In order to investigate the structure in more detail, images of different magnifications were taken and compared. The magnifications of Fig. 9(A) and (B) were 25 and 200, respectively. As shown in Fig. 9(A), even though the granules on the tablet surface were more compressed than those inside, there existed many empty spaces between the granules throughout the tablet where water could be absorbed by capillary forces. It is these pores that increase the absorption of water by capillary forces. At higher magnification (Fig. 9(B)), a detailed distribution of pores can be observed. Upon contact with water or saliva, the granules could easily dissociate, and the whole tablet disintegrated to form a paste, which could be easy to swallow. The disintegration time was very short (between 10 and 30 s). As the compression pressure increased, the pores became smaller (Fig. 9(C) and (D)). When the compression pressure was higher than 500 lbs, the porous structure of the tablets was especially hard to observe.

4. Conclusions

As the resin particles became smaller, the time needed to reach equilibrium was shorter than that of bigger particles and also the drug release rate increased due to the increased surface area of the resin complexes. Further sustained release could be obtained by applying various aqueous polymeric dispersions on the resin complexes by the Wurster process. When the drug release profiles were applied into the Boyd model, linear Bt–t plots were obtained suggesting that drug diffusion within the matrix is the rate-controlling step. The plot of M as a function of $t^{1/2}$ also resulted in a linear relationship, suggesting that diffusion is rate-controlling. Increasing the coating thickness by applying greater amounts of polymer dispersion is one way to reduce the diffusion rate through the coating. Unlike to EC, Kollicoat® SR30D coated particles could be compressed into tablets without any rupture or cracks on the coating due to the better mechanical properties of the polymer. This resulted in no significant changes in release rates. SEM showed the mechanical strength of the polymers affected the morphological changes after compression. Therefore, Kollicoat® SR30D was a suitable polymer for the coating of ion-exchange resin complexes, which were granulated and compressed into fast-disintegrating tablets.

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