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The influence of Surelease and sodium alginate on the in-vitro release of tamsulosin hydrochloride in pellet dosage form

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Abstract

The objective of this study was to prepare controlled-release pellets containing 0.2 mg tamsulosin hydrochloride using a pelletizer-equipped piston extruder and double-arm counter-rotating rollers with Surelease and sodium alginate. The release of tamsulosin HCl from pellets coated with the commercial aqueous ethylcellulose dispersion (Surelease) was investigated at different coating loads. In addition, the effect of sodium alginate on drug release was investigated by varying the ratio of sodium alginate to microcrystalline cellulose (MCC). Dissolution studies were first performed in 500 mL simulated gastric fluid (pH 1.2) containing 0.003% (w/w) polysorbate 80 and then in simulated intestinal fluids (pH 7.2). The morphology of pellet surfaces and cross sections were examined by scanning electron microscopy (SEM). Apparently, the spherical pellets were prepared using a pelletizer-equipped piston extruder and double-arm counter-rotating rollers. The release profiles of tamsulosin HCl from Surelease-coated pellets were significantly affected by changing the content of Surelease, the pH of the dissolution medium and the ratio of sodium alginate to MCC. The drug release rates not only decreased with increase in the coating load, but also increased when the pH of the dissolution medium was increased from 1.2 to 7.2 regardless of the sodium alginate-to-MCC ratio. Moreover, the drug release rate at pH 7.2 was gradually increased by increasing the ratio of sodium alginate to MCC. SEM showed smooth surfaces of Surelease-coated pellets. These results suggest that Surelease and sodium alginate would be useful excipients in the preparation of controlled-release pellets with the desired release profiles.

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Introduction

The aim of controlled-release technology is to achieve a predictable and reproducible drug release rate over an extended period of time. Pellets are frequently used in controlled-release systems because they are freely dispersed in the gastrointestinal tract and they offer flexibility for further modification. Pelletization is an agglomerization process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. Most common pelletization processes used in the pharmaceutical industry are extrusion/spheronization, solution/suspension layering and powder layering (Ghebre-Sellassie 1989). Of these processes, extrusion and spheronization is currently used to produce pharmaceutical pellets (Gandhi et al 1999), because of its ability to incorporate high levels of active components without producing an excessively large particle (David 1997). Unfortunately, the formulation aids available for pelletization by extrusion/spheronization are very limited due to the characteristics desired of their wet masses. Microcrystalline cellulose (MCC) is widely used as a pelletization aid because of its ideal physical properties, including moisture retention and distributing ability, important for extrusion/spheronization (Chatlapalli & Rohera 1998). Moreover, the proportion of sodium alginate in formulations significantly influenced the in-vitro dissolution of drug (Chatchawalsaisin et al 2004).

Meanwhile, film coating is an ideal process for the modification of controlled-release dosage forms. Ethylcellulose is the most widely used water-insoluble polymer in film-coating (Iyer et al 1993). This polymer is tasteless, odourless and has the ability to form tough, flexible coatings (Porter 1989). While ethylcellulose was initially used in organic solvent-based solutions, the application of aqueous polymeric dispersions of ethylcellulose, such as Surelease, is commonplace in the pharmaceutical industry and is the method of choice for film coating (Yuen et al 1993; Bodmeier & Paeratakul 1994; Sadeghi et al 2000, 2001, 2003). Majid Khan and colleagues (Majid Khan & Jiabi 1998; Majid Khan & Zhu 1998) also investigated the feasibility of ibuprofen controlled-release tablets by incorporating Surelease as the granulating agent. Moreover, there are a few examples in the pharmaceutical market of coated tablets and coated granules, such as Claversal, Salofalk, Asacolitin and Pentasa (Klotz 1999; Tromm et al 1999; Christensen 2000; Klotz & Schwab 2005).

To investigate the controlled-release pellet formulations of drug, tamsulosin hydrochloride was employed as a model compound. Tamsulosin HCl is a highly selective alpha 1A-adrenoreceptor antagonist that has been used for the treatment of lower-urinary-tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). As compared with other alpha-antagonists, tamsulosin HCl has greater specificity for alpha 1A receptors and does not affect alpha receptors on blood vessels (Beduschi et al 1998; O'Leary 2001). Following oral administration of 0.2–0.4 mg tamsulosin HCl, it is absorbed from the intestine and almost completely bioavailable (Wilde & McTavish 1996). However, many LUTS/BPH patients are elderly and have an impaired cardiovascular regulation. They are particularly at risk for cardiovascular adverse events, which are not only unpleasant, but can also lead to serious morbidity, such as falls and fractures potentially resulting in hospitalization, nursing home placement or death (Chapple & Andersson 2002). Therefore, the preferable formulation of tamsulosin HCl is via controlled release that can modulate the release rate of drug and improve the absorption of drug in the intestinal tract.

Here, we aimed to prepare controlled-release pellets containing tamsulosin HCl (0.2 mg per capsule) using a pelletizer-equipped piston extruder and double-arm counter-rotating rollers with Surelease and sodium alginate. In preliminary studies, Surelease was selected as the granulating agent and coating material. The effect of the ratio of sodium alginate to MCC on in-vitro drug release was investigated.

Materials and Methods

Materials

Tamsulosin HCl was purchased from Yon Sung Fine Chemicals Co. Ltd (99.6% purity, Korea). Poloxamer 407 (Lutrol F127, BASF, Germany), microcrystalline cellulose (MCC, Avicel PH102; FMC, USA), sodium alginate (Duckalgin NSPH; Kibun Food Chemica, Japan), and Surelease (E-7-19010; Colorcon, USA) were used. All organic solvents were of high-performance liquid chromatography (HPLC) grade. All other chemicals were of reagent grade.

Preparation of drug-loaded pellets

To investigate the optimum formulation, the starting composition of pellets consisted of 0.13% w/w tamsulosin HCl, 0.33% w/w poloxamer 407, 26.54% w/w MCC, 19.91% w/w sodium alginate, 26.54% w/w magnesium trisilicate and 26.54% w/w Surelease (by solid), respectively. Briefly, tamsulosin HCl (0.2 mg/capsule) and poloxamer 407 were dissolved in distilled water. The drug/surfactant solution was uniformly mixed with MCC, sodium alginate and magnesium trisilicate. The mixture was then kneaded with Surelease diluted into distilled water in a mixer (Kitchen Aid Inc., MI). To produce controlled-release pellet formulations, Surelease was not only incorporated into the pellet mixture but also spray-coated onto the pellets. The wet mass of drug/excipients was extruded using an oil pressure-extruding machine (3″ motor 2 p, ½ hp; Changsung Industry, Korea) and a piston extruder consisting of a hollow steel cylinder containing a sliding steel piston (Figure 1, left).

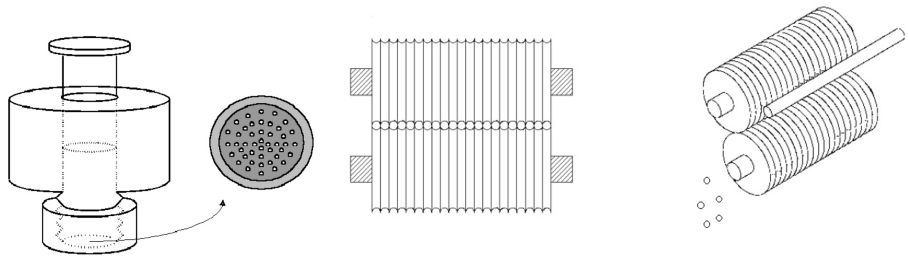

Figure 1 An experimental apparatus used in the extrusion/pelletization process. Piston extruder (left) and double-arm counter-rotating rollers (middle and right). These two rollers had continuous semicircle pits of constant diameter between projective lines, along the plate of roller, and vertically to the axis of rotation. They closely contacted each other and rotated in reverse. When the cylindrical strand was put into the osculating plane of two rollers parallel to the axis of rotation, the strand was revolved by the two rollers, which counter-rotated at different speeds at above (160 rev min^{-1}) and below (80 rev min^{-1}). Subsequently, the strand was cut off by the projective lines and compressed by the semicircle pits. As a result, the cylindrical strand was formed into spherical pellets with constant diameter.

The length of the die was 10 mm and the diameter 1.2 mm. The extrudates were put into double-arm counter-rotating rollers (3″ motor 2 p, ½ hp; Changsung Industry) with different speeds at above (160 rev min^{-1}) and below (80 rev min^{-1}). Then, the cylindrical strand was shaped into spherical pellets with constant diameter (Figure 1, middle and right). The spherical pellets were dried in a 60°C drying oven for 24 h.

Coating procedure

Surelease was diluted to 15% w/w dispersion, based on the manufacturer's recommendations, by adding distilled water while stirring. For coating, 100-g quantities of tamsulosin HCl-loaded pellets from the 1000–1190-μm sieve fraction were used. The drug-loaded pellets were coated using a coating pan (HS Spray System; Han Sung Engineering, Korea) with Surelease to different thicknesses equivalent to theoretical weight gains of 10, 15, 17, 20 or 25% w/w. The temperature and rotating speed of the coating pan were maintained at 55–60°C and 50–60 rev min^{-1} during the coating process. Meanwhile, the coating solution was applied at a rate of 2–5 mL min^{-1}. Following coating solution application, the pellets were dried in a coating pan for an additional 30 min to keep the pellets from sticking. The Surelease-coated pellets were spread onto paper trays and stored at 60°C for 24 h. Drug release from Surelease-coated pellets was investigated before and after curing.

Drug analysis

The concentration of tamsulosin HCl was determined by high-performance liquid chromatography (HPLC) method. The HPLC system consisted of a pump (Model 600; Waters, USA), an auto-sampler (Model 717 plus; Waters), and a UV detector (Model 486 Tunable Absorbance Detector; Waters). The C_{18} reverse-phase column (Xterra, 5 μm, 4.6 mm × 250 mm, Waters) was used at room temperature. The mobile phase consisted of acetonitrile (50%) and 0.02% perchloric acid (50%) adjusted to pH 2.0 with 1.0 M NaOH and the flow rate was 0.8 mL min^{-1}. The injection volume was 100 μL. The signal was monitored at 225 nm.

Assay of drug content

A quantity (about 2 g) of each pellet formulation was ground into fine powder using a mortar and pestle. An accurate amount of powder (800 mg) was placed in 500 mL of phosphate buffer (pH 7.2) and sonicated for 1 h. The mixture was centrifuged at 3000 rev min^{-1} for 5 min after stirring violently for 2 h. A 10-mL volume of supernatant was transferred into a 20-mL tube. One millilitre of 0.5 M HCl and 2 mL of internal standard solution (20 μg mL^{-1} of propyl paraben in 50% acetonitrile) were added to the supernatant and the solution was vortex mixed for 1 min. The mixtures were then filtered using a 0.45-μm syringe filter (PTFE; Whatman Inc., NJ) and analysed by HPLC.

Dissolution studies

The release of tamsulosin HCl from Surelease-coated pellets was performed according to the USP XXV paddle method using a dissolution apparatus (Vankel VK7000; Cary, NC). The Surelease-coated pellets containing 0.2 mg of tamsulosin HCl were filled into hard gelatin capsules (capsule no. 3; Su-Heung Capsule Co. Ltd, Korea). The capsules were added into 500 mL of simulated gastric fluid without pepsin (adjusted to pH 1.2 with HCl) containing polysorbate 80 (0.003%, w/w) at 37 ± 0.1°C and with a paddle speed of 100 rev min^{-1}. To avoid capsule flotation, a sinker was used. Each sample (5 mL) was withdrawn at defined time intervals, and the same volume of simulated gastric fluid was compensated. Two hours after incubation in simulated gastric fluid, 500 mL of simulated intestinal fluids without pancreatin (pH 7.2, phosphate buffer according to the USP without enzyme) was added into the vessel to adjust the pH 1.2 of medium to pH 7.2. Samples were taken and simulated intestinal fluid was added to compensate the volume. One millilitre of internal standard solution (4 μg mL^{-1} propyl paraben in 50% acetonitrile) was added to the 5-mL sample withdrawn at pH 1.2. Meanwhile, 0.5 mL HCl (0.5 M) and 1 mL internal standard solution were added to the 5-mL sample withdrawn at pH 7.2. Each sample was vortexed for 1 min and filtered with a 0.45-μm syringe filter (PTFE; Whatman Inc., NJ). Then, the filtrate was analysed by HPLC. Dissolution test were repeated six times for all formulations except in the curing study (n = 12) and then the drug percentage released over time was calculated.

Kinetic mechanism

The kinetics of tamsulosin HCl release from 20% w/w Surelease-coated pellets at various ratios of sodium alginate to MCC was determined by fitting the dissolution data to distinct models:

$$Q_t = K_0 t + Q_0 \quad (1)$$

$$Q_t = Q_\infty (1 - e^{-K_1 (t - t_0)}) \quad (2)$$

$$Q_t = K_2 t^{1/2} + C \quad (3)$$

where Q_t is the amount of drug released at time t, K_0 is the zero-order release rate constant, K_1 is the first-order kinetic rate constant, considering lag time (Kervinen & Ylirusi 1993), and K_2 is the root-time rate constant. Furthermore, the Korsmeyer-Peppas semi-empirical model was applied to understand the corresponding mechanism (Korsmeyer et al 1983):

$$Q_t/Q_\infty = K t^n \quad (4)$$

where Q_t/Q_∞ is the fraction of the drug released at time t, K is the release constant, and n is the release exponent indicating the mechanism of drug release. The optimum values for the parameters presented in each equation were

determined by linear or non-linear least-squares fitting methods using SPSS 10.0 software. A direct non-linear fitting of the experimental result was carried out for each of the mathematical models considered (through minimization of the sum of the squared residuals based on the Levenberg-Marquardt algorithm).

Scanning electron microscopy (SEM)

The morphology of pellet surfaces and cross sections were examined by SEM (S-3000N; Hitachi, Japan). Cross sections of the pellets were obtained by cutting the pellets with a razor blade. The coated pellets were mounted onto stubs using double-sided adhesive tape. The samples were vacuum-coated with gold in an argon atmosphere, and then observed at an accelerating voltage of 15 kV.

Statistical analysis

The effect of the ratio of sodium alginate to MCC on the derived drug release rate was evaluated using a one-way analysis of variance followed by the Student–Newman–Keuls multiple comparison test (SPSS 10.0). A comparison between two of the derived parameters of the models was performed using Student's *t*-test (Yuksel et al 2000). $P < 0.05$ denoted significance in all cases.

Results and Discussion

The dissolution profiles of drug release from Surelease-coated pellets are presented in Figure 2. Uncoated pellets disintegrated in dissolution medium and released 100% drug within 2 h. The pH of the dissolution medium does not seem to have a significant effect on the release rate, whereas the coating load of Surelease increased drug release rate. At higher coating loads, such as 25% coating, only 9.8% of tamsulosin HCl was released in 2 h, whereas those pellets coated to weight increases of 15% and 10% showed 40.1% and 65.3% of drug release in 2 h, respectively. The decrease in release rate with increasing coating load may be attributed to the increased diffusional path length with an increase in the thickness of the coating membrane. The release of drug depends on the thickness of ethylcellulose membranes, as previously reported by many authors (Ozturk et al 1990; Maganti & Celik 1994; Sarisuta & Punpreuk 1994). For 10% w/w Surelease-coated pellets, no gel-like structure remained during the dissolution test. Meanwhile, the 15% and 17% w/w Surelease-coated pellets swelled during the dissolution test, yet retained their spherical gel-like structure. However, the 20% and 25% w/w Surelease-coated pellets remained intact for at least 6 h. Of the excipients used in the preparation of pellets, sodium alginate is a water-soluble excipient, which could create osmotic forces that can break up the membrane barrier. Previously, Majid Khan and colleagues (Majid Khan & Jiabi 1998; Majid Khan & Zhu 1998) reported that water-soluble co-excipients can create osmotic forces that may break up the membranous barrier, resulting in higher release rates of drugs. From the dissolution result, the Surelease membrane was able to endure the osmotic forces from the water-soluble excipient (sodium alginate) for at least 6 h at more than the 20% w/w load in this formulation.

Figure 3 shows the release profiles of tamsulosin HCl from 20% Surelease-coated pellets at various ratios of sodium alginate to MCC. In addition, the parameters of the mathematical models for the data corresponding to drug release up to 2 h and from 2 h to 5 h are summarized in Table 1. After fitting mathematical models to the individual unit dissolution data, the selection was based on comparisons of the following features of the models: higher determination coefficient and smaller residual mean square and *F*-ratio probability. Considering these criteria, the zero-order model best fit the dissolution for data covering both the time up to 2 h and the time between 2 h and 5 h.

The drug release profiles were significantly affected by the sodium alginate-to-MCC ratio. As shown in Figure 3

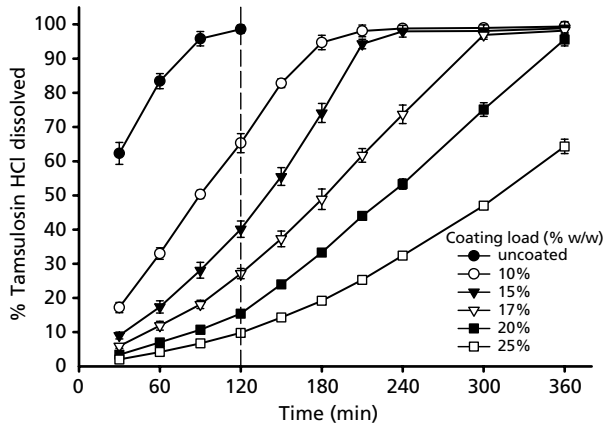

Figure 2 Drug release profiles of tamsulosin hydrochloride from Surelease-coated pellets at different coating loads (dashed line shows the change of medium pH from 1.2 to 7.2). Data are means ± s.d., n = 6.

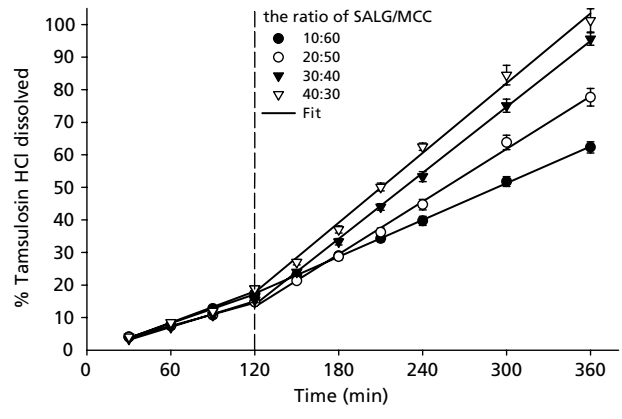

Figure 3 Drug release profiles of tamsulosin hydrochloride from pellets coated with 20% w/w Surelease at various ratios of sodium alginate to microcrystalline (SALG/MCC) (dashed line shows the change of medium pH from 1.2 to 7.2). Data are means ± s.d., n = 6.

Table 1 Parameters of the mathematical models obtained from data corresponding to drug release, with various ratios of sodium alginate to microcrystalline cellulose (20% w/w coating load)

Model	Statistics	10:60	20:50	30:40	40:30
Data corresponding to drug release in the time up to 2 h					
Zero order	K_0 (%min^{-1})	0.15	0.12	0.13	0.16
	s.e.	2.94×10^{-3}	3.01×10^{-3}	4.12×10^{-3}	5.54×10^{-3}
	r^2 (F)	0.9915 (6948)	0.9860 (4984)	0.9792 (2702)	0.9741 (2121)
First order	K_1 (min^{-1})	1.67×10^{-3}	1.30×10^{-3}	1.45×10^{-3}	1.78×10^{-3}
	s.e.	3.70×10^{-5}	3.52×10^{-5}	4.80×10^{-5}	6.90×10^{-5}
	r^2 (F)	0.9893 (5496)	0.9843 (4433)	0.9769 (2421)	0.9682 (1730)
Square root	K_2 (%min$^{-½}$)	2.43	1.93	2.16	2.58
	s.e.	8.59×10^{-2}	7.36×10^{-2}	9.36×10^{-2}	0.13
	r^2 (F)	0.9733 (2191)	0.9690 (2242)	0.9601 (1405)	0.9453 (1000)
Korsmeyer-Peppas	K (%min^{-1})	9.24×10^{-2}	0.14	7.06×10^{-2}	6.96×10^{-2}
	s.e.	1.11×10^{-2}	2.05×10^{-2}	1.42×10^{-2}	1.52×10^{-2}
	n	1.09	0.97	1.12	1.16
	s.e.	2.61×10^{-2}	3.14×10^{-2}	4.37×10^{-2}	4.74×10^{-2}
	r^2 (F)	0.9927 (8019)	0.9854 (4756)	0.9809 (2951)	0.9791 (2634)
Data corresponding to drug release in the time from 2 h to 5 h					
Zero order	K_0 (%min^{-1})	0.19	0.28	0.34	0.39
	s.e.	4.00×10^{-3}	5.99×10^{-3}	4.96×10^{-3}	6.05×10^{-3}
	r^2 (F)	0.9878 (15954)	0.9877 (9042)	0.9941 (18509)	0.9933 (16069)
First order	K_1 (min^{-1})	3.03×10^{-3}	4.72×10^{-3}	6.47×10^{-3}	8.39×10^{-3}
	s.e.	8.50×10^{-5}	1.98×10^{-4}	2.75×10^{-4}	4.12×10^{-4}
	r^2 (F)	0.9804 (9934)	0.9843 (2854)	0.9633 (2955)	0.9682 (2456)
Square root	K_2 (%min$^{-½}$)	5.64	8.37	10.08	11.52
	s.e.	0.14	0.24	0.20	0.21
	r^2 (F)	0.9832 (11604)	0.9779 (5043)	0.9886 (9533)	0.9910 (12040)
Korsmeyer-Peppas	K (%min^{-1})	7.02×10^{-2}	7.80×10^{-3}	8.63×10^{-3}	1.02×10^{-2}
	s.e.	9.53×10^{-3}	1.24×10^{-3}	1.27×10^{-3}	1.97×10^{-3}
	n	1.16	1.58	1.59	1.58
	s.e.	2.48×10^{-2}	2.89×10^{-2}	2.66×10^{-2}	3.49×10^{-2}
	r^2 (F)	0.9881 (162985)	0.9917 (13485)	0.9932 (15944)	0.9883 (9245)

s.e., standard error of model parameter; r^2, determination coefficient; F, F distribution for residual variance analysis ($P = 0.000$).

and Table 1, the drug release rate (K_0) increased when the pH of the dissolution medium was increased from pH 1.2 to pH 7.2 at all ratios ($P < 0.05$). The drug release rates (K_0) increased approximately 1.6, 2.3, 2.6 and 2.4 fold as the ratio of sodium alginate to MCC increased from 10:60 to 40:30 after the dissolution medium was replaced. In addition, analysis of variance showed that there were significant differences among the formulations ($P < 0.001$), which were ranked by the Student-Newman-Keuls test in order of increasing drug release rate as follows: 10:60 < 20:50 < 30:40 < 40:30 (ratio of sodium alginate to MCC). In fact, the drug release rate (K_0) at pH 7.2 gradually increased as the ratio of sodium alginate to MCC increased. It is postulated that the increase in drug release rate at pH 7.2 can be attributed to the nature of sodium alginate, which is a natural hydrophilic polysaccharide derived from seaweed. At neutral pH, sodium alginate is soluble and hydrates to form viscous solutions; however, below pH 3, alginic acid, which swells in water yet is insoluble, is rapidly formed. In general, drug release may be critically influenced by the hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer (Tonnesen & Karlsen 2002). In other words, the sodium alginate swells with hydration but is virtually insoluble; however, the swollen sodium alginate is soluble or eroded when the dissolution medium is replaced with a solution of pH 7.2. In addition, in a preparation made by direct compression of drug–alginate blends, it has been demonstrated that the release rate of a poorly-water-soluble drug is significantly faster in simulated intestinal fluid than in simulated gastric fluid, although the drug solubility is slightly higher in acid than in pH 7.5 buffer (Hodsdon et al 1995). Therefore, considering the very low level of drug loading (0.2 mg per capsule), it is reasonable to believe that the increase in drug release rate caused by the replacement of the pH 1.2 dissolution medium with pH 7.2 medium and by the increase of the sodium alginate-to-MCC ratio might be attributed to the nature of sodium alginate, although drug release kinetics seem to depend on drug solubility and pH of the dissolution medium.

In this study, the Korsmeyer-Peppas model was applied to understand the corresponding mechanism because the release system of pellets consisted of a combination of the matrix system and polymer membrane coating system. Generally, this model is used to analyse the release of pharmaceutical polymeric dosage form when the release mechanism is not well known or when more than one type of release phenomenon could be involved (Costa et al 2001). Values of the exponent n calculated using drug dissolution profiles at pH 1.2 were between 0.97 and 1.16 (Table 1). These values indicate that drug release may be attributed to an apparent zero-order release or a relaxation-controlled process. Furthermore, the values of the exponent n calculated using drug dissolution profiles at pH 7.2 were between 1.58 and 1.59, except for the ratio of 10:60 (n = 1.16), indicating non-Fickian or Super case-II transport (n > 1.0) (Rao et al 1988; Brazel & Peppas 2000). The n values for drug release profiles at pH 7.2 were higher than those at pH 1.2 at every ratio of sodium alginate to MCC ($P < 0.05$). This might be because of the nature of sodium alginate (as mentioned above) and the hydration of the pellets for 2 h before the pH of the dissolution medium was changed to pH 7.2. In fact, the value of the exponent n calculated using drug dissolution profiles (at the ratio of 30:40) at a constant pH of 7.2 was 1.32 (calculated range of $0.1 \leq Q_t/Q_\infty \leq 0.6$), smaller than the exponent n (1.59) calculated above (Figure 4).

The effect of storage on the release of drugs from coated pellets cured at elevated temperatures was investigated for pellets containing tamsulosin HCl coated with 20% (w/w) Surelease. The coalescence of latex particles is often incomplete after the coating process; therefore, a curing step has been recommended with ethylcellulose pseudolatexes to accelerate further coalescence and formation of a homogeneous film (Bodmeier & Paeratakul 1991). In this study, the coated pellets were oven-cured at 60°C for 24 h; the release rate of tamsulosin HCl before and after curing was extremely different

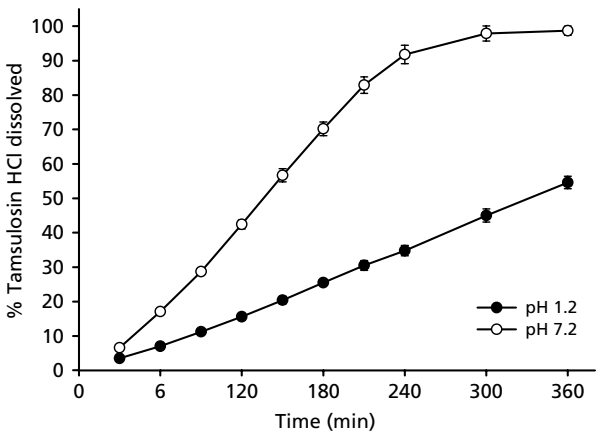

Figure 4 Drug release profiles of tamsulosin hydrochloride from pellets coated with 20% w/w Surelease in a ratio of 30:40 in different pH of dissolution media. Data are means ± s.d., n = 6.

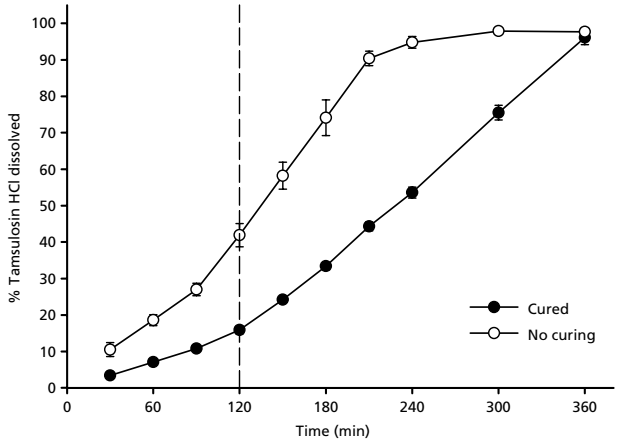

Figure 5 Drug release profiles of tamsulosin hydrochloride from pellets coated with 20% w/w Surelease before and after curing for 24 h at 60°C (dashed line shows the change of medium pH from 1.2 to 7.2). Data are means ± s.d., n = 12.

(Figure 5). The release profiles for coated pellets cured for 24 h at 60°C decreased significantly. The similarity factor (f_2) value for uncured pellets versus 24 h-cured pellets was 26.6. The similarity factor was originally described by Moore & Flanner (1996) and is recommended for dissolution profiles for comparison with the FDA's industrial guidelines (FDA Guidance for Industry 1997a, b). Generally, f_2 values > 50 (50–100) ensure sameness or equivalence of two curves according to these guidelines. Several studies reported that the curing of coated pellets in an oven could cause a decrease in drug release rates. Pearnchob & Bodmeier (2003) have reported that the drug release from pellets sharply decreased after curing for 24 h at 80°C, while no differences were observed between the fluidization temperatures. In addition, the interdiffusion of the (pseudo-)latex particles was not complicated without the curing step in this study (Frohoff-Hulsmann et al 1999).

The surface of uncoated pellets, 17% w/w, and 25% w/w Surelease-coated pellets is presented in Figure 6. As can be seen, the ethylcellulose membrane was formed and the surface of the pellet was found to be smooth with increasing coating loads. In addition, the surface of the uncoated pellet was rough, with some pores and channels apparent on the surface. It is postulated that the morphology of the uncoated pellet is due to the nature of sodium alginate–MCC, which swells in contact with water during preparation of the pellet (particularly in the kneading, extrusion and pelletization processes) and is porous when removing water inside and on the surface of the uncoated pellets during the dry process.

Conclusion

In this study, spherical pellets containing tamsulosin HCl were prepared for controlled release using a pelletizer-equipped piston extruder and double-arm

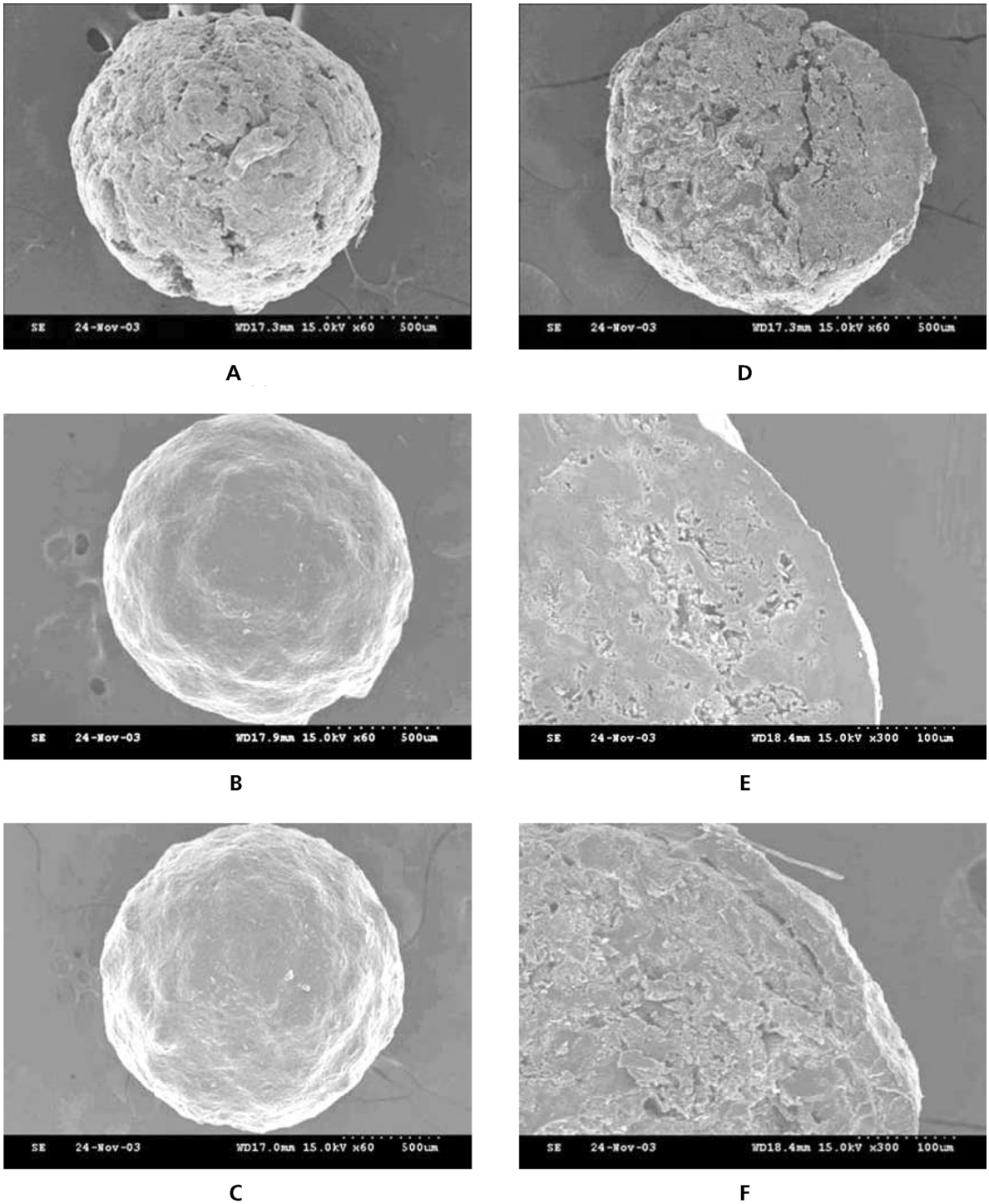

Figure 6 Scanning electron micrographs of tamsulosin hydrochloride pellets: uncoated pellets (A); 17% w/w Surelease-coated pellets (B); 25% w/w Surelease-coated pellets (C); cross sections of A, B and C (D, E and F, respectively).

counter-rotating rollers with Surelease and sodium alginate. There was no significant difference in the drug release rate at pH 1.2. However, the drug release rate gradually increased with increasing the ratio of sodium alginate to MCC at pH 7.2. These results suggest that drug release may be attributed to the natures of sodium alginate, such as pH-dependent solubility and hydration kinetics. In conclusion, the tamsulosin HCl-loaded pellets, prepared by using the extrusion/pelletization method, could be pharmaceutically acceptable for controlled release in the intestine where the drug is completely absorbed.

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