Drug Development and Industrial Pharmacy, 35:26–33, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802144203

informa
healthcare

Development of a Tamsulosin Hydrochloride Controlled-Release Capsule Consisting of Two Different Coated Pellets

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Tamsulosin hydrochloride (TSH) controlled-release capsule (pellets) was successfully prepared using a novel, simple, and flexible multiunit drug delivery system, which consisted of two different coated pellets. The TSH-loaded core pellets consisting of microcrystalline cellulose (MCC), lactose, Carbopol® 974P, and the active agent, were prepared by extrusion/spheronization method. Eudragit® NE30D and Eudragit® L30D-55 were used as the coating materials to prepare sustained-release (SR) pellets and enteric-release (ER) pellets. The coated pellets were prepared using two different equipments: centrifugal coater and fluidized-bed coater. By adjusting the ratio of SR and ER pellets, more than one blend ratios, which meet the in vitro release criterion were obtained. A similarity factor (f_2) was employed to choose the optimum proportion compared with the commercial product (Harnal® capsule). The morphology of the pellet surfaces was examined by scanning electron microscopy (SEM) before and after dissolution. The release profiles were significantly affected by changing the proportions of SR and ER. The optimum ratio is SR:ER = 2:1 using a centrifugal coater (f_2 = 61.93) and SR:ER = 3:1 using a fluidized coater (f_2 = 66.42). This result suggests that blending these two-part pellets (SR and ER) can provide an alternative to preparing a controlled-release dosage form, instead of blending of the coating polymer.

Keywords controlled-release pellets; extrusion/spheronization; tamsulosin hydrochloride; Eudragit® NE30D; similarity factor

INTRODUCTION

Pellets are a multiunit dosage form that is utilized for different controlled-release applications. Extrusion/spheronization is an established technique used in pharmaceutical industry to prepare spherical pellet (Erkoboni, 2003; Reynolds, 1970; Trivedi, Rajan, Johnson, & Shukla, 2007). Pellets have many advantages, for example, they exhibit a homogeneously distribution in the gastrointestinal tract (GIT), provide more stable plasma profiles, reduce the dosing frequency and, importantly, more flexible modification can be applied to obtain the ideal in vitro release profile, compared with the single-unit dosage form (Ghebre-Sellassie, 1989).

Aqueous polymeric dispersions are widely used in the coating of solid dosage forms because they can offer various advantages in comparison with organic solvent-based coating such as reduced toxicity and less environmental concerns (Bobmeier, Guo, & Paeratakul, 1997; Fukumori, 1997; Lecomte, Siepmann, Walther, MacRae, & Bodmeier, 2004). Many of them are commercially available (e.g., the Eudragit® series, Aquacoat® series, Surelease®, and Kollicoat® series). However, usually, classical approaches based on pellets coated with only one single type of these aqueous polymeric dispersions is difficult to produce the desired release profile (Siepmann, Siepmann, Walther, MacRae, & Bodmeier, 2008). Many reports have shown that binary blends of these aqueous dispersions can provide a broad ranges of drug release patterns, and some of them offer special functions, for instance, thermosensitivity (Fujimori, Yonemochi, Fukuoka, & Terada, 2002). A further application is to blend a water-insoluble and an enteric polymer to obtain a pH-sensitive polymer as a coating material (Amighi, Timmermans, Puigdevall, Baltes, & Moes, 1998; Hu, Liu, Tang, & Zhang, 2006; Lecomte, Siepmann, Walther, MacRae, & Bodmeier, 2003; Munday, 2003). In contrast to pH-insensitive polymer blends, the properties of this type of coating are triggered by the pH of the surrounding environment. In this way, when at a low pH, drug release is primarily controlled by diffusion through the intact film coating and, when at a high pH, the leaching of the enteric polymer out of the coating plays an important role (Siepmann et al., 2008).

However, the blended polymers also have some disadvantages: firstly, and the most importantly, is the problem of incompatibility and lack of stability, because aqueous polymeric dispersions are colloidal dispersions and hence very sensitive to external factors (e.g., pH, temperature, presence of a second polymer) and might be destabilized when blend two type of polymer dispersions. It has been pointed out that aqueous dispersions of ethyl cellulose are incompatible with

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hydroxypropyl methylcellulose (HPMC) and may result in flocculation and sedimentation (Sakellariou, Rowe, & White, 1986; Siepmann et al., 2008; Wong & Bodmeier, 1996). Similarly, when blending anionic dispersions (e.g., Eudragit® L, Eudragit® S) with cationic dispersions (e.g., Eudragit® RL, Eudragit® RS), interactions between the ionic groups of the polymers can occur (Siepmann et al., 2008). Secondly, plasticizers can also potentially redistribute from one polymer into the other during curing and/or long-term storage.

Eudragit® NE30D and Eudragit® L30D-55 were chosen as the coating materials to achieve a particular pH-dependent release. Moreover, it is reported that these two polymers (NE30D:L30D-55) were not completely miscible at a ratio less than 4:1 (Zheng & McGinity, 2003). Two parts pellets were prepared with the same core but different coating films: sustained-release (SR) pellets were coated with a water-insoluble polymer (Eudragit® NE30D), whereas extended-release (ER) pellets were coated with an enteric polymer (Eudragit® L30D-55). Then these two parts are blended to obtain the desired drug release kinetics. This particular coating procedure avoids direct contact between the two different types of aqueous polymeric dispersions, thereby avoiding the possible problem of incompatibility. Moreover, it is a simple matter to predict the proportions of these two parts by determining the respective release profiles and the process can be scaled up simply by mixing these two coated pellets in different proportions. Interestingly, only a few studies have been conducted to examine the blending of different coated pellets (Chen & Zhu, 2005; Chen, Zhu, & Cheng, 2007). In current study, a new method of blending the coated pellets instead of blending the coating materials was developed.

Tamsulosin hydrochloride (TSH), a highly selective alpha 1A-adrendoreceptor antagonist that has been used for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) (Beduschi, Beduschi, & Oesterling, 1998; O'Leary, 2001), was employed as a model drug. TSH is a perfect candidate drug for the preparation of a controlled-release dosage form, because it can produce cardiovascular adverse events, which can lead to serious morbidity (Chapple & Andersson, 2002). Therefore, a better formulation of TSH involves controlled release that offers more stable plasma profiles and thus reduces any adverse effects. Many methods have been reported for the preparation of TSH controlled-release pellets (Kim, Jun, Lee, et al., 2005; Kim, Kim, & Hwang, 2007; Kim, Kim, Kang, et al., 2007; Kim, Kim, Park, et al., 2007; Kim, Kim, You, et al., 2007; Kim, Park, Jun, et al., 2005; Kim et al., 2006).

In our study, to investigate the influence of different coating equipment on the coating procedure, a laboratory-scale centrifugal coating and granulating machine (Model BZJ-360M, Beijing Tianmin High Technology Development Co., Beijing, China) and a fluidized-bed coater (Model: FD-MP-01, Powrex Corporation, Itami, Japan) were used.

The objective of this study was to establish a novel, simple, and flexible method of preparing controlled-release pellets.

MATERIALS AND METHODS

Materials

TSH (99.5% purity) was obtained from the pharmaceutical chemistry laboratory of Shenyang Pharmaceutical University. Microcrystalline cellulose (MCC) (Avicel PH101, Huzhou Zhanwang Pharmaceutical Co., Ltd, Huzhou, China), Carbopol® 974P (Batch No.:CC58NAB704, Neveon Inc., Cleveland, OH, USA), lactose (Wyndale, NZMP Ltd., Wellington, New Zealand), methacrylic acid copolymers (Eudragit® NE30D and Eudragit® L30D-55, Röhm-Pharma GmbH Chemische Fabrik, Darmstadt, Germany), polyethylene glycol (PEG-6000, Beijing Huiyou Fine Chemicals, Beijing, China), talc (Guangxi Yulin Talc Factory, Yulin, China), micronized silica (Huzhou Zhanwang Pharmaceutical Co., Ltd, Huzhou, China), No. 3 hard gelatin capsules (Coni-snap, Suzhou Capsule Co., Suzhou, China) were used. Commercially available controlled-release TSH capsule (Harnal, 0.2 mg/capsule, Yamanouchi Pharmaceutical Co. Ltd., Japan) was chosen for comparison. All organic solvents were of high-performance liquid chromatography (HPLC) grade. All other chemicals were of reagent grade.

Manufacture of Drug-Loaded Pellets by Extrusion/Spheronization

The drug-loaded pellets contained 0.11% (wt/wt, based on the core pellets) TSH, 74.89% MCC, 20% lactose, and 5% Carbopol® 974P. Briefly, the calculated amounts of TSH were dissolved in a suitable quantity of distilled water (after supersonication); the drug-loaded solution was thoroughly mixed with MCC, lactose, and Carbopol® 974P then kneaded to obtain a wet mass. The wet mass was then extruded through a 1.0-mm screen at 60 rpm and spheronized at 500 rpm for 20 min using laboratory-scale extrusion/spheronization equipment (Model: WL350 Centrifugation Pelletizer, Wenzhou Pharmaceutical Machine Factory, Wenzhou, China). The obtained pellets were dried at 40°C for 24 h and the pellets ranged in size from 0.6 to 0.9 mm.

Coating and Mixing Procedure

Coating of Sustained-Release Pellets

Table 1 summarizes the composition of coating dispersions for a batch of 500 g uncoated core pellets; briefly, micronized talc (particle size: 6.5 μm, 50%, wt/wt, based on the dry polymer weight) was dispersed in purified water and homogenized in a high-speed disperser (Ultra Turrax® T18 basic, IKA® Group, Staufen, Germany) for 10 min. Then the desired amount of Eudragit® NE30D was added, stirred by a magnetic stirrer (HJ-4, Guohua Group, Changzhou, China) for 30 min, and adjusted to the final volume with purified water to produce a coating suspension with a total solid content of 15% (wt/wt), according to the manufacturer's guidelines. The coating was performed using two frequently used pieces of coating equipment: a fluidized-bed coater and a laboratory-scale centrifugal

TABLE 1
Composition of Coating Dispersions (For a Batch of 500 g Uncoated Core Pellets)

	Coating Level (SR Pellets) (%)				Coating Level (ER Pellets) (%)			
	4	6	8	10	4	6	8	10
Eudragit® NE30D	66.7 g	100 g	133.3 g	166.7 g	—	—	—	—
Eudragit® L30D-55	—	—	—	—	66.7 g	100 g	133.3 g	166.7 g
Talc	10 g	15 g	20 g	25 g	5 g	7.5 g	10 g	12.5 g
PEG-6000	—	—	—	—	2 g	3 g	4 g	5 g
Water	123.3 g	185 g	246.7 g	308.3 g	106.3 g	159.5 g	212.7 g	278.3 g
Polymer content (%, wt/wt)	10	10	10	10	11.1	11.1	11.1	11.1
Solid content (%, wt/wt)	15	15	15	15	15	15	15	15

coating and granulating machine. The coating parameters were as follows (room temperature = 20°C):

Fluidized-bed coater: batch size = 500 g; inlet temperature = 25°C; air flow = 60 m^3/h; spray pressure = 1.2 MPa; and spray rate = 3 g/min.

Centrifugal coater: batch size = 500 g, rotational speed of plate = 150 rpm; blower rate = 10 × 15 L/min; air flow rate = 15 L/min; spray air pressure = 0.5 MPa; spray rate = 3 g/min.

During the coating process, the coating dispersion was stirred continuously. The pellets were coated until a theoretical weight gain of 4, 6, 8, and 10% (wt/wt) was obtained. After coating, the pellets were spread on trays, uniformly mixed with 0.5% micronized silica to avoid the tack problem during the curing process and the trays were put into an oven for 24 h at 40°C to ensure completion of the curing, based on the manufacturer's recommendations.

Coating of Enteric-Release Pellets

According to Table 1, micronized talc (25%, wt/wt) and PEG-6000 (10%, wt/wt based on dry polymer weight) were dispersed in purified water and homogenized for 10 min, then the desired amount of Eudragit® L30D-55 was added, stirred for 2 h and adjusted to a final volume (15%, wt/wt, total solid content). The operating parameters are almost identical except that the coating temperature needed is 40°C. The pellets were coated until a theoretical weight gain of 5 and 10% (wt/wt) was obtained. The post-process treatment was the same as described above.

Assay of Drug Content

The samples were assayed by HPLC. An Agilent 1100 HPLC was used (G1379A Degasser, G1311A QuatPump, G1313A ALS auto-sampler, G1315B DAD detector, Agilent Technologies, Palo Alto, CA, USA) fitted with a C_{18} reverse-phase column (HiQ sil C18W, KYA TECH Corporation, Tokyo, Japan) operated 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, the flow rate was 0.8 mL/min. and the injection volume was 20 μL. The detector wavelength used was 225 nm (Kim, Jun, Lee, et al., 2005).

From each batch of coated pellets, a suitable amount (4 g) was taken and ground into a fine powder using a mortar and pestle. Then, about 1 g of the powder was accurately weighed, placed into a 50-mL volumetric flask, 20 mL NaOH solution (0.05 mol/L) was added, and the mixture was sonicated for 30 min. After cooling to room temperature, the solution was neutralized with 5.5 mL HCl solution (0.2 mol/L). Finally, the solution was diluted with acetonitrile to 50 mL and then passed through a 0.45-μm membrane filter. The filtrate was then analyzed by HPLC.

Drug Release Studies

In vitro drug release studies were carried out using USP XXVII Type 2 dissolution apparatus (paddles method) with a ZRS-8G Intelligent Dissolution Tester (Tianjin University Radio Factory, Tianjin, China) at a speed of 100 rpm. In this method, 500 mL simulated gastric fluid (SGF) without pepsin (adjusted to pH 1.2 with HCl) containing polysorbate 80 (0.003%, wt/wt), as the dissolution medium, was placed in the glass vessel of the assembled apparatus, and the dissolution medium allowed to equilibrate at 37 ± 0.1°C. The coated pellets containing 0.2 mg TSH were transferred to hard gelatin capsules and then added to the dissolution medium with a sinker. At predetermined intervals, 5 mL samples were withdrawn and immediately replaced with an equal volume of SGF (maintained at 37 ± 0.1°C). Two hours after incubation in SGF, 500 mL of the simulated intestinal fluid without pancreatin (37°C, pH 7.2, phosphate buffer without enzyme) was added to the vessel and the pH of the medium increased from 1.2 to 7.2. The samples were filtered (0.45 μm) and analyzed by HPLC as described above, using an injection volume of 100 μL.

Pellet Morphology

Morphological examination of the surface of the core pellet and coated pellets was carried out using scanning electron microscopy (SEM) (Model: SSX-550, Shimadzu, Kyoto, Japan).

The samples were mounted onto stubs using double-sided tape and coated with of gold under an argon atmosphere using a gold sputter coater before observation; the accelerating voltage is 5 kV.

Treatment of Dissolution Data

Several methods have been described for the comparison of dissolution profiles (Costa, 2001; De Castro et al., 2006; Ma, Wang, Liu, & Tsong, 2000; Polli, Rekhi, Augsburger, & Shah, 1997; Williams & Liu, 2000). In our study, mean dissolution time (MDT) and similarity factor were used. The MDT was calculated from Equation 1 (Polli et al., 1997):

$$\mathrm{MDT} = \frac{\sum_{i=1}^{n} t_{\mathrm{mid}} \Delta M}{\sum_{i=1}^{n} \Delta M}, \qquad (1)$$

where t_{mid} is the time at the midpoint between i and $i - 1$, and ΔM is the additional amount of drug dissolved between i and $I - 1$.

The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test and reference product over all time points (Moore & Flanner, 1996):

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\}, \qquad (2)$$

where log denotes logarithm based on 10. The scale-up and post approval changes for immediate-release/modified-release dosage forms guidances (SUPAC-IR/MR) suggest that an f_2 value between 50 and 100 be required to conclude similarity of two dissolution profiles. Only one time point after reach 85% of dissolution was used to calculate f_2 to avoid bias (Shah, Tsong, Sathe, & Liu, 1998).

A pairwise procedure of individual dissolution profiles was used to calculate the f_2 values. All MDT values were calculated for each individual dissolution profile. Statistical analysis (one-way ANOVA) was performed using the SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences were considered to be significant at the level of $p < .05$.

RESULTS AND DISCUSSION

For Sustained-Release Pellets

According to the dissolution criteria of TSH controlled-release pellets, the drug release percentages at 2, 3, and 5 h were restricted to 12–39%, 44–70%, and more than 70%, respectively, whereas the pH of the dissolution medium changed from 1.2 to 7.2 at 2 h. The profiles of TSH released from SR pellets are shown in Figure 1. As can be seen, the accumulated drug release decreased significantly with the increase in coating weight gain regardless of the coating equipment. This can be easily explained by the increased diffusional path length with an increase in the thickness of the polymer coat (Maganti & Çelik, 1994). Table 2 summarizes the MDT and similarity factor (f_2) of SR pellets coated by different coating equipments. At 4 and 6% coating level, the MDT of SR pellets coated with fluidized-bed coater differed significantly from the pellets coated with centrifugal coater ($p < .01$). Whereas at 8 and 10% level, the drug release is slightly different but statistically identical ($p > .05$), $f_2 > 50$ indicated that the average difference between these two dissolution profile is no more than 10% at any sample time points (Shah et al., 1998). It

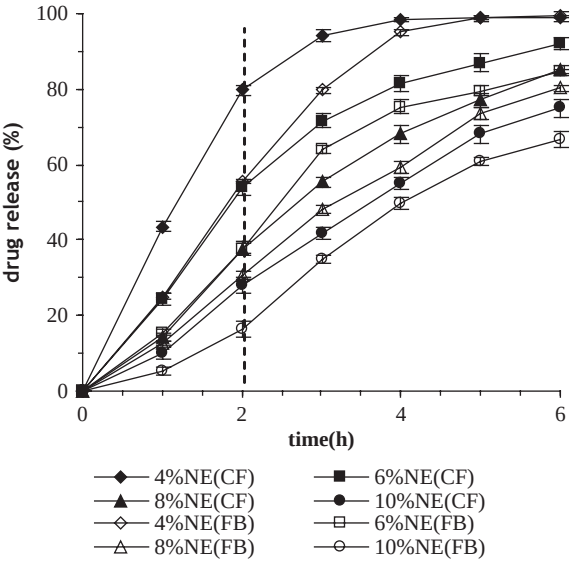

FIGURE 1. Drug release profiles from Eudragit® NE30D-coated pellets (SR pellets) at different coating levels using different coating equipment: a centrifugal coater (CF) and a fluidized-bed coater (FB). (The dashed line shows the change in medium pH from 1.2 to 7.2, $n = 6$.)

TABLE 2
The Mean Dissolution Time (MDT) and Similarity Factor (f_2) of SR Pellets Coated by Different Coating Equipments (Mean ± *SD*, $n = 6$)

Coating Level (%)	MDT (h)		f_2[a]
	CF	FB	
4	1.31 ± 0.08	1.94 ± 0.10**	35.3 ± 1.9
6	2.04 ± 0.15	2.30 ± 0.07**	51.6 ± 4.3
8	2.53 ± 0.19	2.71 ± 0.08	60.5 ± 5.5
10	2.80 ± 0.10	2.98 ± 0.18	57.9 ± 4.8

CF, centrifugal coater; FB, fluidized-bed coater.
[a]Dissolution profiles were matched according to identical dissolution kettle number.
**Indicate the different is very significant ($p < .01$, cf. CF).

also stated that such a variety of equipment often adds an extra degree of complexity to the scale-up process (Porter, 2006).

Interestingly, for the 4, 6, and 8% weight gain, the pellet coat breaks and falls off after 3 h in pH 7.4 PBS, as can be seen in Figure 2. The proportion of breaking decreased as the coating weight gain increased. Meanwhile, the 10% coats remained intact throughout the dissolution testing. Of the excipients used in the preparation of the pellets, lactose is a water-soluble material, whereas Carbopol® 974P is an acrylic acid polymer. At low pH, the carboxylic acid groups of the Carbopol molecules would be uncharged and should only undergo weak interactions. In addition, the molecules are in the coiled form, in near neutral or alkaline media, so that carboxylates are formed and negatively charged molecules repel each other and extreme expansion occurs, making Carbopol swell in alkaline medium. The use of Carbopol in extruded and spheronized beads has been described (Neau et al., 2000). The coating polymer film in pH 1.2 medium was intact after 2 h indicating that the osmotic force created by the lactose solute (Marucci, Ragnarsson, & Axelsson, 2007) is not sufficient to break the coat, and the swelling character of Carbopol® 974P at pH 7.4 is considered to be the main reason for rupture of the coat barrier. Eudragit® NE30D, a polymer composed of methyl methacrylate and ethyl acrylate monomers in a ratio of 2:1, has a low glass transition temperature (T_g) about 9°C (data was given by Pamela Böhmann, Evonik-Degussa Company, Document code: VB 07/067, July 2006, according to DIN EN ISO 11357). In the room temperature (about 25°C), the polymeric films prepared from Eudragit® NE30D are soft and flexible (Lehmann, 1997; Zheng & McGinity, 2003). The pellets coated with it can even be compressed into tablets without cracking the coat. Such flexibility increased with the coating level in our study. In our study, the coat was able to tolerate the swelling force from the swellable excipient (Carbopol® 974P) for at least 6 h at a coat level more than 10% (wt/wt) in this formulation (see Figure 2D). The influence of coat breaking on drug release is not investigated in our research.

However, as shown in Figure 1, only using Eudragit® NE30D as the coating material means that it is not possible to obtain the desire drug release profile, and only 45% was released within 3 h and 65% at 5 h. This problem can be solved by addition of ER pellets in the following study.

For Extended-Release Pellets

Figure 3 shows the release profiles of ER pellets. In the first 2 h, the percentage of TSH released decreased with the increase in the coating level and, at 2 h, drug release was reduced to 5% when the coat gain was 10%. In basic medium, the drug release increased sharply. This can be attributed to the enteric solubility of Eudragit® L30D-55 that is a methacrylic acid copolymer. Films prepared from it are insoluble in gastric fluid but are readily soluble in aqueous media with a pH above 5.5. The SEM

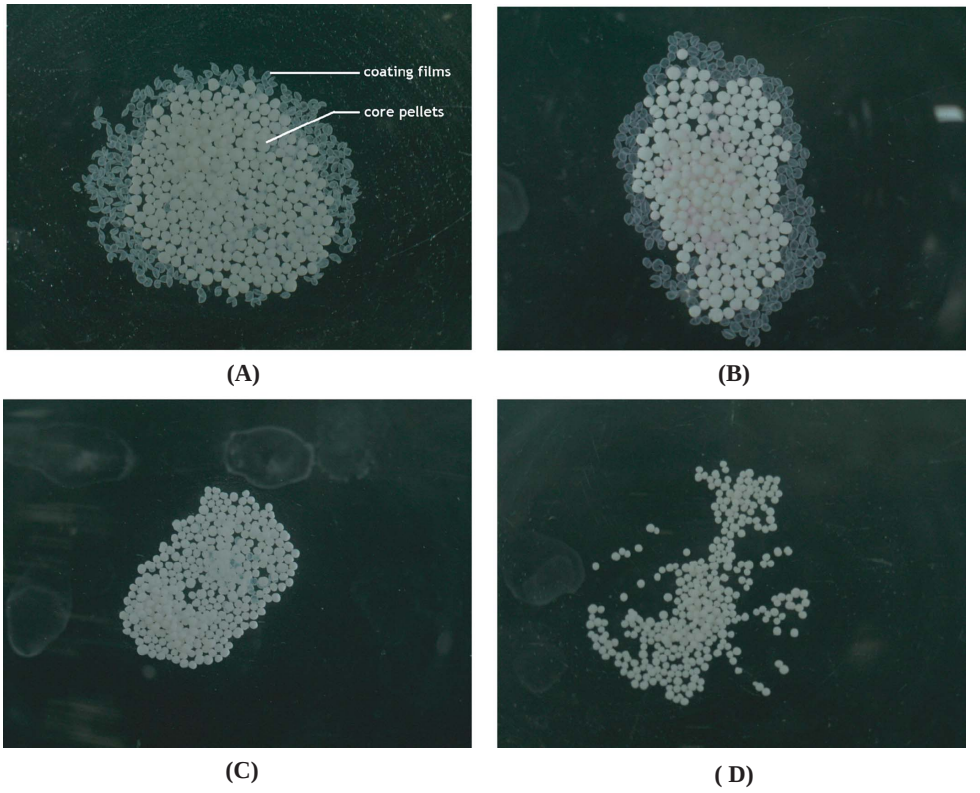

FIGURE 2. Effect of coating level on the coating film (Eudragit® NE30D) state after dissolution: (A) 4%, (B) 6%, (C) 8%, and (D) 10%.

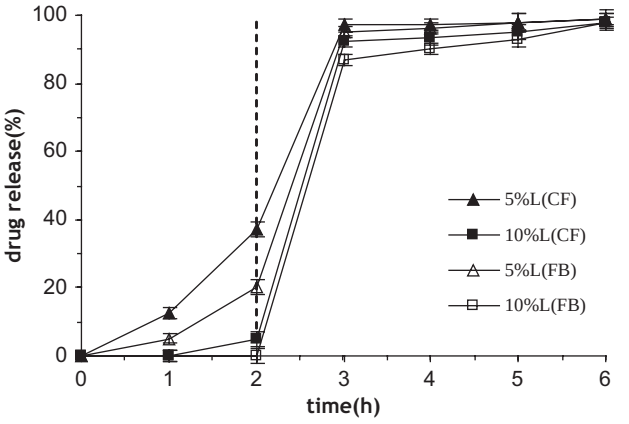

FIGURE 3. Drug release profiles from Eudragit® L30D-55 coated pellets (ER pellets) at different coating levels using different coating equipment: a centrifugal coater (CF) and a fluidized-bed coater (FB). (The dashed line shows the change in medium pH from 1.2 to 7.2, $n = 6$.)

image (see Figure 6D) also confirms this result. The polymer film of the ER pellet disappears after dissolution testing.

For a Mixture of Sustained-Release and Extended-Release Pellets

Because the final pellets consist of these two-part pellets, the final drug release profiles can be predicted from the following equation:

$$\mathrm{DR}\% = \frac{R_A \times P_A \times C_A + R_B \times P_B \times C_B}{P_A \times C_A + P_B \times C_B}, \qquad (3)$$

where DR% is the percentage drug release of mixed pellets at each sample time, R_A is the percentage drug release of SR pellets, P_A is the blend proportion of SR part, C_A is the drug content of SR pellets, and R_B, P_B, and C_B have the same meaning as R_A, P_A, and C_A.

Figure 4 shows the drug release profiles from mixed pellets consisted of different proportions of SR and ER, using a centrifugal coater. The greater the proportion of ER part, the lesser drug release at 2 h, and the more drug release after 2 h; this is due to the enteric solubility of ER pellets. As can be seen in Figure 5, the MDT of the actually release profile and the predicted one are almost identical ($p < .05$). The similarity factor (f_2) is 82.86 ± 3.54, which means that the average difference between these two dissolution profile is no more than 3% at any sample time points (Shah et al., 1998). This demonstrates that the release of pellets consisting of different proportions of SR and ER pellets is predictable and controllable.

Table 3 summarizes the similarity factor (f_2) of different proportions. The optimum proportion is chosen simply by

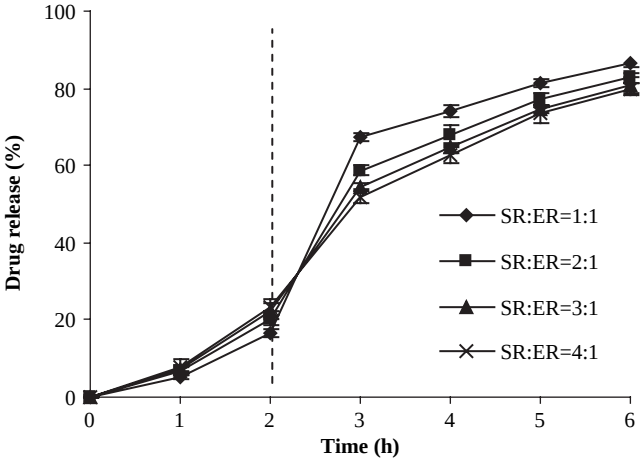

FIGURE 4. Drug release profiles from mixed pellets consisting of different proportions of SR pellets (10%NE30D) and ER pellets (10%L30D-55), using a centrifugal coater. (The dashed line shows the change in medium pH from 1.2 to 7.2, $n = 6$.)

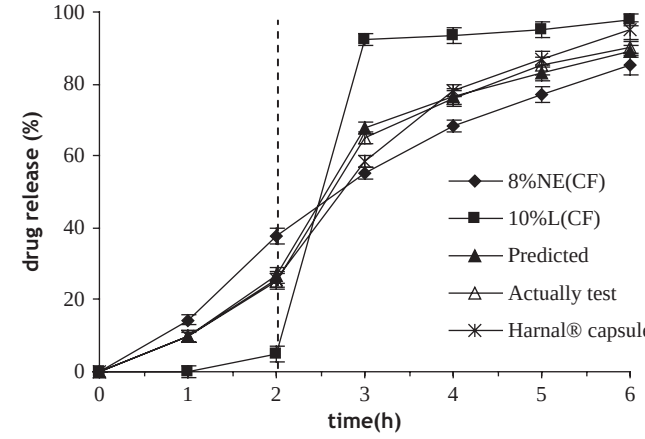

FIGURE 5. Drug release profiles of SR pellets, ER pellets, the mixture, and the Harnal® capsule. (The dashed line shows the change in medium pH from 1.2 to 7.2, $n = 6$.)

TABLE 3
The Similarity Factor (f_2) of Mixed Pellets Consisting of Different Proportions (Reference Sample is the Harnal® Capsule)

Proportion of Pellets	f_2
Centrifugal coater	
SR: ER = 1:1	57.67
SR: ER = 2:1	61.93
SR: ER = 3:1	58.66
SR: ER = 4:1	55.85
Fluidized-bed coater	
SR: ER = 1:1	62.95
SR: ER = 2:1	66.35
SR: ER = 3:1	66.42
SR: ER = 4:1	64.33

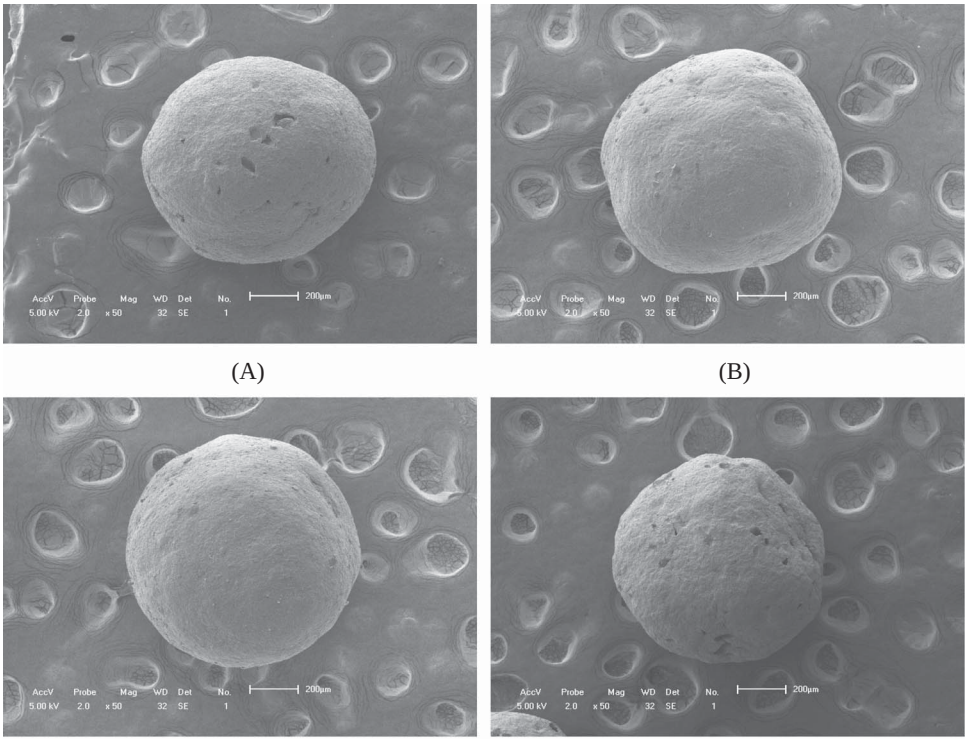

FIGURE 6. Scanning electron micrographs of pellets: uncoated pellets (A); 10% (wt/wt) Eudragit NE30D-coated pellets (B); 10% (wt/wt) Eudragit L30D-55-coated pellets (C); 10% (wt/wt) Eudragit L30D-55-coated pellets after dissolution test (D).

comparing the value of the similarity factor (f_2). According to this theory, the optimum proportion is SR:ER = 2:1 using the centrifugal coater (f_2 = 61.93) and SR:ER = 3:1 using the fluidized coater (f_2 = 66.42).

The surface of uncoated pellets, SR and ER pellets (before and after dissolution test) is presented in Figure 6. As can be seen, the surface of the uncoated pellets has some pores on the surface due to the dehydration effect of the excipients during the drying process (Kim, Jun, Lee, et al., 2005). The pores disappear on the surface of coated pellets (SR and ER pellets) and the surface is smoother. The surface of ER pellets after dissolution testing is the same as the uncoated pellets indicating that the polymer coat of ER pellets is dissolved in the dissolution medium (pH 7.2).

CONCLUSION

In this study, a new method of blending the coated pellets instead of blending the coating materials was developed to prepare TSH controlled-release pellets. MDT and similarity factor (f_2) were used to compare the difference of two dissolution profiles. This method proved to be predictable and controllable. Both the centrifugal coater and the fluidized-bed coater can be used successfully to prepare TSH controlled-release pellets, indicating that this method can be easily applied on an industrial scale. Using this method, not only can pH-sensitive pellets be prepared by blending a water-insoluble part and an enteric-soluble part, but it also can be used in other applications, such as blending the two parts of pellets with different drug release rate, the desired drug release profiles can be obtained when the mixing proportion is appropriate.

ACKNOWLEDGMENT

The authors would like to thank Evonik-Degussa Company for technical support and supplying samples.

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