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Pseudoephedrine Hydrochloride Sustained-Release Pellets Prepared by a Combination of Hot-Melt Subcoating and Polymer Coating

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Pseudoephedrine hydrochloride is an active very highly water soluble substance. In order to control release of a drug with this property, we developed the application of a combination of hot-melt subcoating and polymer coating was developed. The main objective was to investigate the influence of this combination on the release of highly water soluble drug and how it works. Hot-melt subcoating was achieved by using a coating pan. Subsequently, the outer polymer coating was prepared by fluidized bed, and the drug release was determined by high-performance liquid chromatograph (HPLC) method. Hot-melt subcoating can form a barrier between the drug-loaded pellets and the polymer coating layer, which prevents migration of the drug during film application. Consequently, the level of polymer coating can be reduced significantly, and the effectiveness of the polymer coating increased. In this study, the release profile of pellets with a 10% hot-melt subcoating and 5% polymer coating weight gain met the dissolution requirement of USP29 for pseudoephedrine hydrochloride extended-release capsules. Compared with pellets only polymer coated (10% level), the polymer coating level of pellets prepared by this technology was reduced by half due to hot-melt subcoating. By means of this hot-melt subcoating and polymer coating, sustained-release pellets containing pseudoephedrine hydrochloride were successfully prepared.

Keywords pseudoephedrine hydrochloride; hot-melt subcoating; polymer coating; sustained-release pellets; fluidized bed

INTRODUCTION

Multiple-unit sustained-release dosage forms such as pellets are considered to be superior to single-unit ones for therapeutic advantages. They can distribute into gastrointestinal tract (GIT) homogeneously therefore reducing the peak plasma fluctuation, avoiding dose dumping, minimizing irritation to the GIT, increasing the compliance of the patients, and improving the safety and efficacy of active substance.

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According to the requirements of pseudoephedrine hydrochloride extended-release capsules in USP29, sustained-release pellets were prepared. Currently, sustained-release method includes water-insoluble polymer coating such as ethyl cellulose dispersion (Sadeghi, Ford, Rubinstein, & Rajabi-Siahboomi, 2000; Umprayn, Chitropas, & Amarekajorn, 1999), ion exchange resins (Zeng, Cheng, Pan, Zhong, & Huang, 2007), water insoluble or soluble matrix (i.e., stearic acid or HPMC) (Phaechamud & Ritthidej, 2007), and osmotic agents forming osmotic pump (Heng, Hao, Chan, & Chew, 2004). However, the technique mentioned above can be employed in specific dosage forms or active ingredients with specific property. Pseudoephedrine hydrochloride is very highly water soluble. At present, pellets containing drugs with this property are prepared by the melt pelletization process (Hamdani, Moe¨s, & Amighi, 2002), the natural polymer and cross-linking technique (Garcia & Ghaly, 1996), and polymer subcoating (Bruce, Kelong, & McGinity, 2003; Guo, Heinamaki, & Yliruusi, 2002). Extremely water soluble drugs needed higher polymer coating levels than poorly soluble ones, because of the migration during the application of the aqueous polymer dispersion (Frenning, Tunón, & Alderborn, 2003; Li & Feld, 1997; Ozturk, Ozturk, Palsson, Wheatley, & Dressman, 1990). This may create pores or channels on the surface or inner part of the pellets during dissolution. For compounds with this property, higher coating levels are required to prevent premature drug release.

Subcoating (Allen, Popovich, & Ansel, 2005; Bruce, Petereit, Beckert, & McGinity, 2003; Crotts, Sheth, Twist, & Ghebre-Sellassie, 2001; Felton et al., 1995; Matthews & Vergilio, 1989) has been proposed as a method to improve the release of extremely water soluble agents. In this study, instead of polymeric subcoating, hot-melt subcoating was applied to retard drug release. It functions as a barrier between the polymer coating layer and the drug-loaded pellets in the film coating, and is intended to reduce media penetration during dissolution. Hot-melt subcoating is a better alternative to polymer subcoating. Film coating requires a solvent, such as water, organic solvent, or a mixture of these, and this may lead to environmental problems, solvent residues, and expensive recovery

costs. Also, the polymer dispersion generally prolongs the length of the coating possess. Obviously, hot-melt subcoating can avoid all these disadvantages.

At present, the hot-melt subcoating reported in the literature has always used a fluidized bed (Barthelemya, Laforeˆta, Faraha, & Joachimb, 1999; Sinchaipanid, Junyaprasert, & Mitrevej, 2004), but in this study, it was carried out using a traditional coating pan. This reduced production costs and saved time as well as labour compared with the technique mentioned above.

Subsequently, Eudragit® NE30D was used for polymer coating by the fluidized bed technique. Eudragit® NE30D is a polymer composed of methyl methacrylate and ethyl acrylate monomers in the ratio of 2:1 (Zheng & James, 2003). It can form a water-insoluble and pH-independent membrane (Lehmann, 1997), which efficiently encapsulates pellets to control drug release. In the current study, the main objective was to investigate the effectiveness of the combination of hot-melt subcoating and polymer coating to control the drug release of an extremely water soluble agent. And also, the hot-melt subcoating can enhance the function of polymer coating as well as the roundness of pellets, which can be confirmed by scanning electron microscope (SEM) photographs. The mechanism of drug release from pellets prepared by the combination of hot-melt subcoating and polymer coating was approached.

MATERIALS AND METHODS

Materials

Pseudoephedrine hydrochloride was donated by Xi An De Tian Pharmaceutical Co. Ltd. (Xi'an, China) Microcrystalline cellulose (Avicel PH 101, MCC) and hydroxypropyl methyl cellulose (HPMC, HT-E5) were purchased from Huzhou Zhan Wang Pharmaceutical Co. Ltd. (Huzhou, China) and octadecanol was supplied by Godrej Industries Ltd. (Mumbai, India) Talc (Guangxi Yulin Talc Factory) was used as anticohesive agent. The subcoating material stearic acid was purchased from Tianjin Bo Di Chemical Engineering Ltd. (Tianjin, China) Eudragit® NE30D dispersions were purchased from Röhm GmbH, Darmstadt, Germany.

Preparation of Drug-Loaded Pellets

Drug-loaded pellets of different formulations are listed in Table 1. The pseudoephedrine hydrochloride, MCC (molecular sponge absorbing water to enhance forming of pellets), which works as accelerant for pellets as well as diluents, and octadecanol were mixed by sieving method of 80 mesh. And the mixture was sieved for three times. The mixture of powder and binder solution (3%, wt/wt, aqueous solution of HPMC) was blended until a wet mass was obtained. Then, the wet mass was extruded using a Granulator (WL350, Wenzhou Pharmacy Equipment Factory, Wenzhou, China) with a 1.0-mm screen on a laboratory scale (500 g). Extruded material was transferred to a spheronizer (WL350, Wenzhou Pharmacy Equipment Factory). A spheronizer speed of 1,000 rpm and spheronization time of 20 min were used to prepare the drug-loaded pellets. Finally, the pellets were dried in a hot air oven at 40°C for 12 h, and then sized using 16–24 mesh.

TABLE 1
Drug-Loaded Pellet of Different Formulations

Formulation No.	Pseudoephedrine Hydrochloride (g)	Octadecanol (g)	MCC (g)
F1	250	100	150
F2	300		200
F3	250	125	125

Hot-Melt Subcoating

In order to control the release of the pseudoephedrine hydrochloride, which is extremely water soluble, we used hot-melt subcoating. Stearic acid (melting point 60°C) was selected for subcoating. The course of hot-melt subcoating is as follows: the temperature of the air chest of the coating pan (B-300 Coating Pan, BaoJi JianHua Co. Ltd., Baoji, China) was set at 80°C (inlet temperature, and the outlet temperature was 40°C), which is slightly higher than the melting point of stearic acid, and the rotation speed of the coating pan was set at 30 rpm. A batch of sized pellets (16–24 mesh) was transferred to the coating pan, and the particles were rolled evenly with the pan. The coating pan has a diameter of 30 cm, and it can deal with the amount of pellets ranging from 300 to 500 g. Heating was continued until the temperature of the particles was above 60°C. At this time, stearic acid was added to the coating pan. The amount of stearic acid was controlled by the weight gain of pellets, such as 5% (wt/wt) of pellets. On a laboratory scale, this quantity of stearic acid can be added in within 10 min in a constant rate. The stearic acid can be divided into several batches. The next batch was added in only when the last one was melted completed. Compared with the amount of pellets, stearic acid was little; therefore, through rolling stearic acid can disperse evenly into pellets, which avoid the agglomerating of melting stearic acid. The stearic acid melted quickly, and rolled over with the particles, coating them uniformly. After all the stearic acid was transferred and melted, and kept rolling for 10 min, the heating apparatus including the air chest was turned off. Subsequently, talc needed to be added to avoid some particles aggregating, because it acts as an anticohesive agent. And the talc was added in gradually. Because the contacting area of pellets was large when rolling in coating pan, and the stearic acid was tacky in liquid state, generally, 3% level (wt/wt of pellets) talc was needed (more than usual, 1%). But if the amount of talc cannot separate pellets, keep adding in until the amount of talc equals to the stearic acid, which would absolutely separate the pellets. Rolling was continued until the temperature fell normally, so that the stearic acid coagulated over the particles.

Polymer Coating

Polymer dispersion spreading on the surface of the pellets forms a plastic film coating. In this study, Eudragit® NE30D was selected for polymer coating. Because the polymeric film prepared by Eudragit® NE30D was soft and flexible, no plasticizer was required (Li & Feld, 1997). The polymer aqueous dispersion was diluted to 15% based on polymer weight. A batch of 300 g pellets, which had been already subcoated with stearic acid, was transferred to the fluidized bed coater (FD MP-10, Powrex Co. Ltd., Osaka, Japan). The pressure of the spray gun was set at 1 MPa, and the rotation speed of the peristaltic pump was set at 0.8–1.2 g/min. According to the instructions of the manufacturer (Röhm GmbH), who provided the Eudragit® NE30D, the temperature was set at 23–25°C. After application of the polymer coating, the pellets were cured at 40°C for 24 h.

Dissolution Study

According to USP29, a dissolution test was carried out using the dissolution apparatus II (paddle), with 900 mL distilled water equilibrated at 37 ± 0.5°C. Coated pellets containing 180 mg pseudoephedrine hydrochloride were transferred to the dissolution medium, and 4 mL samples were withdrawn using an autosampler at 0.5, 1, 2, 3, 4.5, 6, 8, 10, 12 h. And at each time point, six samples were withdrawn by the autosampler. According to chromatographic system of pseudoephedrine hydrochloride extended-release capsules of USP26, the undiluted sample solution was assayed by HPLC at a wavelength of 254 nm, and the mobile phase was a mixture of methanol and ammonium acetate solution (1 in 250) (18:2) at a flow rate of 0.7 mL/min. The column was Nucleosil silica column. The dissolution requirements of USP29 are listed in Table 2.

Pellet Morphology

The surface of the drug-loaded pellets and hot-melt subcoated pellets and the cross-sectional view of the final polymer-coated pellets were recorded by scanning electron microscopy (Model SHIMADZA SSX-550, Kyoto, Japan). Samples were coated with gold before the microscopic determination using ion sputtering.

TABLE 2
Dissolution Requirements of Pseudoephedrine Hydrochloride Extended-Release Capsules in USP 29

Time (h)	Amount Dissolved
3	Between 20 and 50%
6	Between 45 and 75%
12	Not less than 75%

TABLE 3
Particle Size Distribution of Resultant Pellets

Sieve Number	16	18	20	24
Weight Percentage	18.6%	37.5%	38.5%	5.4%

Particle Size Distribution

Particle size distribution was determined by sieve analysis. One hundred grams of resultant pellets were put on the top of the sieve with a series of openings with diameters 1.59, 1.41, 1.27, to 1.06 mm (namely, 16, 18, 20, to 24 meshes). The results were reported as percentage of weight retained on each sieve size (Table 3).

Bulk Density and Tapped Density

The bulk density and tapped density were determined from the weight of 50 g resultant pellets charged into 100-mL glass graduated cylinder, and the volume was recorded. The bulk density was 0.65 g/mL. Then the pellets were tapped until a constant volume was obtained. And the tapped density of resultant pellets was 0.70 g/mL.

The Angle of Repose of Pellets

Fifty gram of resultant pellets were filled into a funnel with a 6-mm internal stem diameter fixed on a clamp. The angle of repose was 20°C, which demonstrated that the flow property of resultant pellets was fairly good.

RESULTS AND DISCUSSION

Influence of Matrix

Octadecanol is a hydrophobic compound, and through extrusion it can form a matrix to reduce the rate of water penetration, thereby preventing the drug coming into contact with the dissolution medium, retarding drug release. The contribution of octadecanol to the reduced drug release rate was investigated. Pellets were prepared by F1 and F2, respectively, and they were both hot-melt subcoated and polymer coated at the same level. This showed that the drug release rate was quite different for the two formulations. The former was much slower than the latter. Subsequently, the proportion of octadecanol was increased to 25% in F3, which was 5% more than that in F1. It was found that the drug release rate fell further compared with F1 when they were hot-melt subcoated and polymer coated to the same degree (as shown in Figure 1). However, the proportion of octadecanol in the formulation should not be too high. Because the melting point of octadecanol was similar to that of stearic acid, pellets will collapse if the proportion of octadecanol in the formulation is too high when hot-melt subcoating is carried out. Consequently, octadecanol is essential and plays a significant role in retarding drug

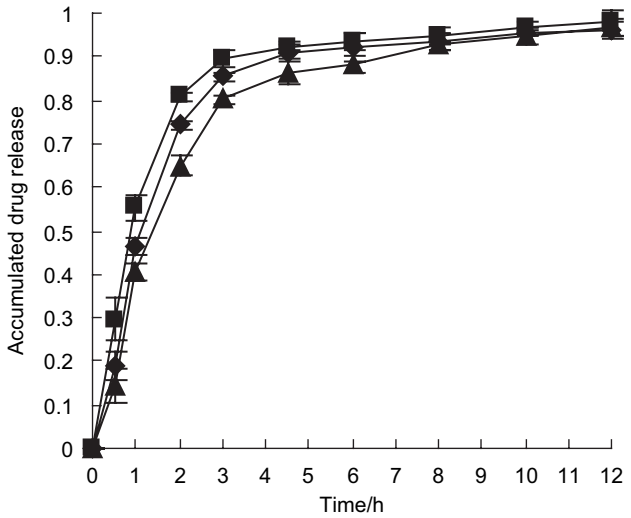

FIGURE 1. Drug release from pellets prepared by different formulations but with the same hot-melt subcoating level of 3% and a polymer coating level of 5%. ■, pellets prepared by F2; ◆, pellets prepared by F1; ▲, pellets prepared by F3.

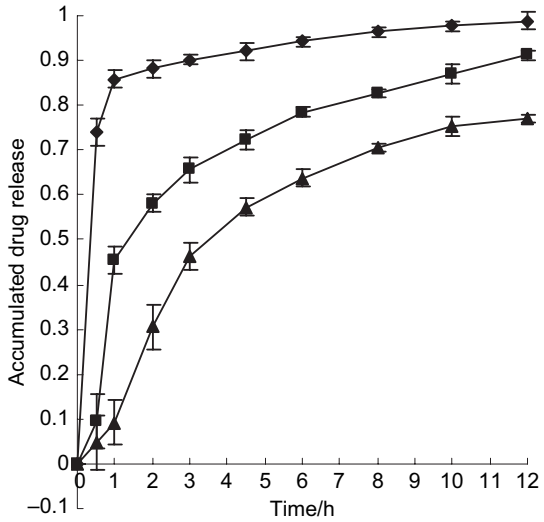

FIGURE 2. Influence of polymer coating on drug release of pellets prepared by F3. ◆, 3% polymer coating level; ■, 7% polymer coating level; ▲, 10% polymer coating level.

release, but it should be at the right rate. Because of the advantages offered by F3, it was selected for further studies.

Influence of Polymer Coating

Pseudoephedrine hydrochloride is extremely water soluble, and drug release from core pellets without any coating layer is fast, reaching 90% within 1 h. Consequently, a polymer coating was introduced to investigate the effect on retarding drug release. Drug-loaded pellets prepared from F3 were polymer coated with Eudragit® NE30D at different coating levels of 3, 7, and 10%. The release profiles are illustrated in Figure 2. It can be seen that the drug release from polymer-coated pellets depended to a great extent on the coating levels of the polymeric dispersion applied to the core pellets. On increasing the polymer coating layer, drug release was reduced. Compared with the requirement of USP29, polymer coating levels of 3 and 7% were unsatisfactory. Because pseudoephedrine hydrochloride is an extremely water soluble drug and the polymer dispersion contains a large amount of water (30% polymer dispersion was diluted to 15% based on the polymer weight), drug migration occurs during the polymer coating process, resulting in pores or channels producing fast drug release profile. As shown in Figure 2, a polymer coating level of 3% cannot completely control drug release, which easily reached 80% and above during 1 h. Even drug-loaded pellets with a 7% polymer coating cannot sustain drug release, and premature release occurred during 1 h. When a 10% level was used, this appeared to meet the requirements of USP29, but during the later period of dissolution, the remaining drug scarcely dissolved in the surrounding medium. This can be attributed to the greater thickness of polymer layer which increased the diffusional path length or, maybe, remnants sticking to the membrane. In addition, on an industrial scale, a 10% polymer coating level would be too high because of involving an increase in time required as well as increasing production costs. Consequently, the hot-melt subcoating was selected to deal with the extremely water-soluble drug, pseudoephedrine hydrochloride.

Influence of Hot-Melt Coating

Hot-melt coating was used as it is more time-saving and cheaper than traditional film coating. This technology provides pellets with sustained-release characteristics. In this study, pellets containing pseudoephedrine hydrochloride prepared from F3 were hot-melt coated at different levels, 5, 10, and 15% (wt/wt) of pellets, by pan coating with stearic acid. The amount of stearic acid or the thickness of hot-melt coating layer was just calculated by pellets weight gain. The drug release profile of pellets coated by the hot-melt process mentioned above is illustrated in Figure 3. The results show that there was an inverse relationship between the thickness of the hot-melt coating and the rate of drug release. However, when hot-melt coating was at the 15% level, the remaining drug could not dissolve totally during late period of dissolution. Compared with the fluidized bed process, this can be attributed to the use of the coating pan. Before hot-melt coating, pellets were heated in a coating pan for a long period, which may have led to various structures for the pellets which contained 25% octadecanol. Subsequently, the hot-melt coating materials were also transferred and rolled along with the pellets for some time. During hot-melt coating, the wax materials were in liquid form, which made them penetrate the surface of pellets to a greater extent than in the case of the fluidized bed process. Also, the liquid stearic acid comes into close contact with the drug, and on cooling, the drug

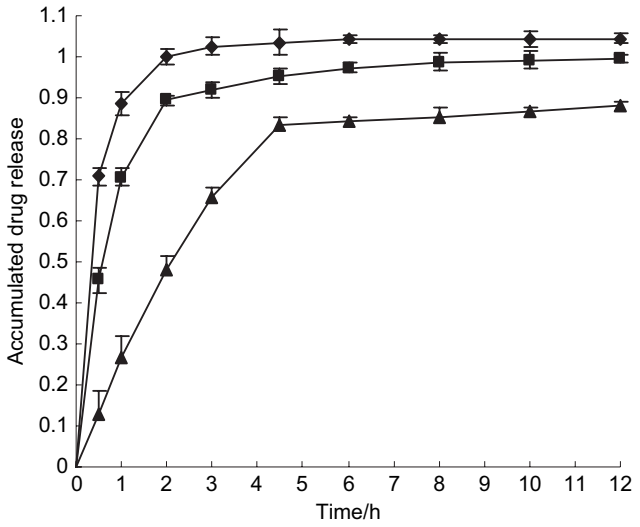

FIGURE 3. Influence of hot-melt coating on drug release of pellets prepared by F3. ◆, 5% hot-melt coating weight gain; ■, 10% hot-melt coating weight gain; ▲, 15% hot-melt coating weight gain.

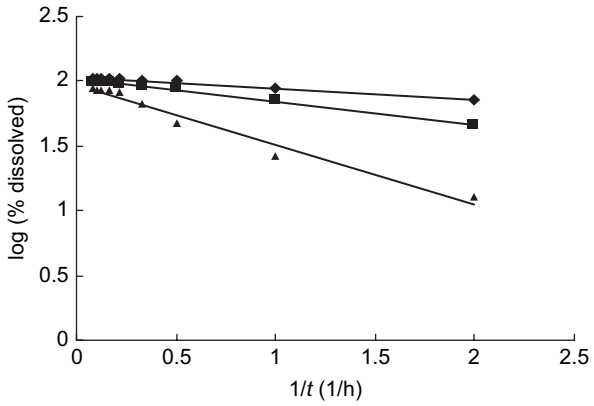

FIGURE 4. Log of the % dissolved from pellets prepared by F3 with hot-melt coatings of different levels versus reciprocal of time. ◆, 5% hot-melt coating level; ■, 10% hot-melt coating level; ▲, 15% hot-melt coating level.

adheres to the hot-melt coating materials strongly, preventing dissolution.

Nuttanan (Sinchaipanid et al., 2004) reported that the release profile of pellets with a hot-melt coating followed none of the conventional models, e.g., first order, zero order, and Higuchi's models. However, he found that the plots of the log of percentage of drug dissolved versus the reciprocal of time yielded straight lines. These were represented as $D_t = D_\alpha e^{-k/t}$ or $\ln D_t = \ln D_\alpha - k/t$, and $\log D_t = \log D_\alpha - k/2.303t$, where D_t and D_α are the concentrations of drug dissolved at time t and infinity, respectively, and k is a constant. However, this equation was deduced based on a 35% or higher level of hot-melt coating. In this study, pellets prepared by F3 with hot-melt coatings of 5, 10, and 15% were investigated to verify whether or not the dissolution profile were acceptable. The linear regression analysis is illustrated in Figure 4. It appears that, although different hot-melt coating equipment was used, the dissolution profiles were similar. The linear relationship is acceptable.

Although hot-melt coating was used, it was still unable to reduce the drug release rate sufficiently. However, the sustained release produced by the hot-melt coating was effective and promising. Consequently, it is recommended that the combination of hot-melt subcoating and polymer coating may work when controlled drug release of an extremely water soluble agent is required. Clearly, hot-melt subcoating is an alternative for polymer coating and this will significantly reduce production costs and save a great deal of time.

Influence of a Combination of Hot-Melt Subcoating and Polymer Coating

The combination of hot-melt subcoating and polymer coating was carried out based on the study discussed above. Pellets prepared from F3 were hot-melt subcoated at the 10% level and polymer coated at the 3, 5, and 7% weight gain level, and a comparison of their drug release is illustrated in Figure 5. It can be seen that pellets with a hot-melt subcoating level of 10% and a polymer coating of 5% weight gain achieved the same effectiveness as those with a polymer coating 10% level (Figure 2). Also, at 12 h, the release from hot-melt subcoated pellets was more complete than that from pellets with only a polymer coating. However, pellets with a 10% hot-melt subcoating and a polymer coating of 3 and 7% weight gain both failed to satisfy the dissolution requirements of USP29. A fast drug release profile was observed in the former, and the latter did not dissolve completely. During the later period of dissolution, the remaining drug cannot be released completely in the case of pellets hot-melt coated at the 10% level and polymer

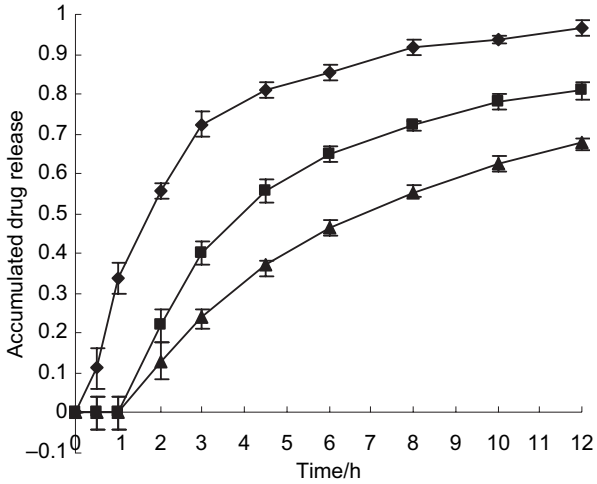

FIGURE 5. Comparison of drug release between pellets prepared by F3 with a hot-melt subcoating level of 10% and different polymer coating levels: ◆, 3% polymer coating; ■, 5% polymer coating; ▲, 7% polymer coating.

coated at the 5 and 7% levels. Even after 24 h, the conditions still did not change. This may be because the stearic acid penetrated deeply into the inner part of the drug-loaded pellets during the hot-melt subcoating process and adhered to some of the drug, preventing its dissolution. Also, during the later period of dissolution, the remaining drug may be deposited on the two membranes. These two reasons contribute to the incomplete dissolution profile. In addition, there was a lag time in the drug release, possibly because at initial release, no channel agents were in the two coating layers, and therefore, the dissolution medium required time to penetrate the two membranes. It is likely that a mixture with the correct proportion of drug-loaded pellets and coated pellets will modify the release profile.

However, the mechanism of drug release of pellets prepared by this technology may differentiate from pellets prepared by hot-melt coating or polymer coating only. To determine drug release model, we investigated four classical ones such as zero order, first order, square root (Higuchi), and Nuttanan models. The results of dissolution tests were fitted to 1–3 and the Nuttanan model.

$$Q = Kt \tag{1}$$

$$Q = e^{Kt} \tag{2}$$

$$Q = Kt^{1/2} + C \tag{3}$$

Where Q is the percentage of drug release at time t, and K is a constant. Correlation coefficients R of the fits of drug release data to different kinetic models are shown in Table 4.

TABLE 4
Drug Release Rate Constants K and Correlation Coefficients R Obtained from Data Corresponding to Pellets Prepared by F3 with Hot-Melt Subcoating 10% Level and Polymer Coating 3, 5, and 7% Weight Gain, Respectively

Model	3%	5%	7%
Zero Order			
R	0.9059	0.9283	0.9715
K	0.0353	0.0543	0.0535
First Order			
R	0.8714	0.8571	0.8983
K	0.0456	0.1091	0.1472
Square Root			
R	0.9468	0.9652	0.9927
K	0.1813	0.2776	0.2686
Nuttanan			
R	0.9969	0.9980	0.9990
K	–0.5555	–0.1374	–1.7529

It is suggested that the Higuchi/square root time model and the Nuttanan model are probably the suitable model for the release rate. And the correlation coefficients were accepted. The release profile of pellets prepared by a combination of hot-melt subcoating and polymer coating still satisfied with the Nuttanan model. It demonstrated that the two membranes, hot-melt subcoating and polymer coating, both play a significant role in prolonging drug release. Namely, when drug dissolved through the sealing coat, it was controlled by the hot-melt subcoating layer. Subsequently, polymer membrane became the main factor on controlling drug release. Also, with the increasing of polymer coating layer, the kinetic model gets more access to Higuchi's model. Because the hot-melt coating layer was low (10%, compared with Nuttanan's report), it cannot form uniform membrane which leads to unregulated release characteristics. As discussed above, pellets prepared by hot-melt coating 10% level just fitted to the model of Nuttanan. However, it happened to satisfy with Higuchi's model when employed the combination of hot-melt subcoating and polymer coating. This is because the polymer dispersion can prepare even membrane based on the hot-melt subcoating, which results in well membrane control drug release. As depicted in Table 4, 7% polymer coating layer was quite suitable to the square root model. Consequently, the main function of hot-melt subcoating can be attributed to three aspects: avoiding migration of the drug during polymer coating, retarding the drug release, and enhancing the effectiveness of polymer coating.

If there is no hot-melt subcoating, relying only on the polymer coating cannot sustain drug release. The failure of the polymer coating may be attributed to the migration of the extremely water soluble pseudoephedrine hydrochloride into the polymer coating during film application. Then there would be deposition on the outer part of the pellets or in the film layer, changing into pores or channels on being dissolved, and leading to more contact between the dissolution medium and the drug. This would finally result in premature drug release (as shown in the release curve). Even a high level of polymer coating (7%) or a polymer coated twice, which would prevent migration, is still unable to control the drug release. However, with the presence of a hot-melt subcoating, the conditions are totally different. Because of the presence of a hydrophobic subcoating, dissolution medium had difficulty in wetting and crossing this layer. During dissolution, the medium should first pass through the film coating layer, then through the hot-melt subcoating layer, and finally reach the core pellets and dissolve the drug. This results in an increased diffusional path length, or the drug solution has to diffuse through two membranes (as shown in the SEM photograph, Figure 6C) before it dissolves in the surrounding medium. Clearly, this is sufficient to sustain drug release. In some cases, such as preparing pellets containing extremely water soluble drugs, if the polymer coating level is too high (such as 10% or above), hot-melt subcoating would be an alternative. As mentioned above, this can reduce production costs and also save time while remaining as effective.

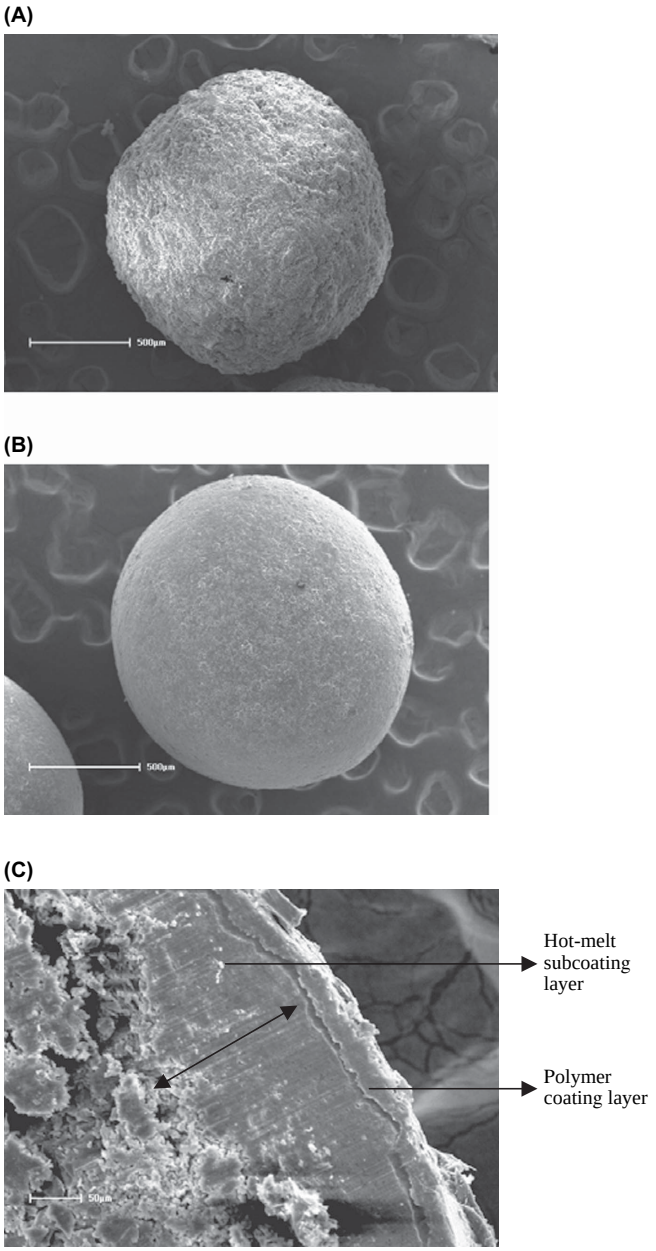

FIGURE 6. (A) SEM photograph of a drug-loaded core pellet prepared by F3. (B) SEM photograph of a pellet prepared by F3 and hot-melt coated at the 10% level without polymer coating. (C) SEM photograph of a cross-sectional view of a pellet prepared by F3 with a hot-melt subcoating level of 10% and polymer coating 5% weight gain.

Hot-melt subcoating not only reduces the drug release rate, but it also enhances the effectiveness of the polymer coating. As illustrated in the SEM photographs, pellets hot-melt subcoated (Figure 6B) were smoother than drug-loaded pellets (Figure 6A). However, in the Nuttanan study (Sinchaipanid et al., 2004), they found that hot-melt coated pellets were not as spherical as uncoated ones. They attributed this to the premature solidification of molten wax droplets and the nonuniform coating pattern of the top spray coater of the fluidized bed. Compared with the fluidized bed, the use of a coating pan is an advance. During the hot-melt subcoating process, molten wax such as stearic acid is constantly in a fluid state because the temperature is at or above its melting point. Rolling along with the drug-loaded pellets, molten stearic acid can spread uniformly on the surface of the pellets. When the temperature is reduced, under the action of surface tension, the stearic acid cools down and shrinks gradually. Finally, the molten wax adapts to the shape of the smooth surface, making the pellets more spherical. As illustrated in Figure 6C, the thickness of hot-melt subcoating layer was uneven, and this is due to the molten stearic acid filling in the holes in the surface of drug-loaded pellets. This confirms the ability of hot-melt subcoating process to increase the roundness of the pellets. During film coating, a lot of the polymer dispersion will enter the holes in the surface of the pellets if there is no smooth subcoating, and this will give a nonuniform membrane, leading to the excessive consuming of the polymer dispersion. However, in the presence of a smooth hot-melt subcoating layer, the polymer dispersion can form a homogenous film, making it more effective, and giving it a better sustained-release profile.

CONCLUSION

Clearly, hot-melt subcoating indeed enhances the effectiveness of polymer coating, avoids the migration of drug during polymer coating, and sustains drug release. All of these make contribution to decrease polymer coating level. Pseudoephedrine hydrochloride sustained-release pellets were successfully prepared by combination of hot-melt subcoating and polymer coating. Drug-loaded pellets prepared by F3 (50% pseudoephedrine hydrochloride, 25% MCC, 25% octadecanol) with a hot-melt subcoating level of 10% and a polymer coating with Eudragit® NE30D at the 5% level met the requirements of USP29 pseudoephedrine hydrochloride extended-release capsules.

Pseudoephedrine hydrochloride pellets hot-melt subcoated in a coating pan with stearic acid were produced. Also, during hot-melt subcoating, the coating pan was found to be superior to the fluidized bed when scaling up the process to industrial proportions. Hot-melt subcoating is promising for sustained release, and is an alternative to polymer coating or polymer subcoating. This novel technique is time-saving and reduces production costs. More significantly, it is a new way of reducing the release rate of extremely water soluble drugs. Drugs with high water solubility can be prepared as sustained-release dosage by using the hot-melt subcoating process.

REFERENCES

Allen, L. V., Jr., Popovich, N. G., & Ansel, H. C. (2005). *Ansel's pharmaceutical dosage forms and drug delivery systems* (8th ed., pp. 265–266). Lippincott Williams & Wilkins.

Barthelemya, P., Laforeˆta, J. P., Faraha, N., & Joachimb, J. (1999). Compritol ® 888 ATO: An innovative hot-melt coating agent for prolonged-release drug formulations. *Eur. J. Pharm. Biopharm., 47*, 87–90.

Bruce, L. D., Koleng, J. J., & McGinity, J. W. (2003). The influence of polymeric subcoats and pellet formulation on the release of chlorpheniramine maleate from enteric coated pellets. *Drug Dev. Ind. Pharm., 29*, 909–924.

Bruce, L. D., Petereit, H. J., Beckert, T., & McGinty, J. W. (2003). Properties of enteric coated sodium valproate pellets. *Int. J. Pharm., 264*, 85–96.

Crotts, G., Sheth, A., Twist, J., & Ghebre-Sellassie, I. (2001). Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble organic acid. *Eur. J. Pharm. Biopharm., 51*, 71–76.

Felton, L. A., Haase, M. M., Shah, N. H., Zhang, G., Infeld, M. H., Malick, A. W., et al. (1995). Physical and enteric properties of soft gelatin capsules coated with Eudragit L30D-55. *Int. J. Pharm., 113*, 17–24.

Frenning, G., Tunón, Å., & Alderborn, G. (2003). Modelling of drug release from coated granular pellets. *J. Control. Release, 92*, 113–123.

Garcia, A. M., & Ghaly, E. S. (1996). Preliminary spherical agglomerates of water soluble drug using natural polymer and cross-linking technique. *J. Control. Release, 40*, 179–186.

Guo, H. X., Heinamaki, J., & Yliruusi, J. (2002). Amylopectin as a subcoating material improves the acidic resistance of enteric-coated pellets containing a freely soluble drug. *Int. J. Pharm., 235*, 79–86.

Hamdani, J., Moe¨s, A. J., & Amighi, K. (2002). Development and evaluation of prolonged release pellets obtained by the melt pelletization process. *Int. J. Pharm., 245*, 167–177.

Heng, P. W. S., Hao, J., Chan, L. W., & Chew, S. H. (2007). Influences of osmotic agents in diffusion layer on drug release from multilayer coated pellets. *Drug Dev. Ind. Pharm., 30*, 213–220.

Lehmann, K. (1997). Chemistry and application properties of polymethacrylate coating systems. In J. W. McGinity, (Ed.), *Aqueous polymeric coatings for pharmaceutical dosage forms* (2nd ed., pp. 101–176). New York, Basel, Hong Kong: Marcel Dekker, Inc.

Li, S. P., & Feld, K. M. (1997). The effect of polymer coating systems on the preparation, tableting, and dissolution properties of sustained-release drug pellets. *Drug Dev. Ind. Pharm., 23*, 623–631.

Matthews, J. W., & Vergilio, G. (1989). Process for coating gelatin capsules, US Patent Issued on March, 28.

Ozturk, A. G., Ozturk, S. S., Palsson, B. O., Wheatley, T. A., & Dressman, J. B. (1990). Mechanism of release from pellets coated with an ethylcellulose-based film. *J. Control. Release, 14*, 203–213.

Phaechamud, T., & Ritthidej, G. C. (2007). Sustained-release from layered matrix system comprising chitosan and xanthan gum. *Drug Dev. Ind. Pharm., 33*, 595–605.

Sadeghi, F., Ford, J. L., Rubinstein, M. H., & Rajabi-Siahboomi, A. R. (2000). Comparative study of drug release from pellets coated with HPMC or sure-lease. *Drug Dev. Ind. Pharm., 26*, 651–660.

Sinchaipanid, N., Junyaprasert, V., & Mitrevej, A. (2004). Application of hot-melt coating for controlled release of propranolol hydrochloride pellets. *Powder Tech., 141*, 203–209.

Umprayn, K., Chitropas, P., & Amarekajorn, S. (1999). Development of terbutaline sulfate sustained-release coated pellets. *Drug Dev. Ind. Pharm., 25*, 477–491.

Zeng, H.-X., Cheng, G., Pan, W. -S., Zhong, G.-P., & Huang, M. (2007). Preparation of codeine-resinate and chlorpheniramine-resinate sustained-release suspension and its pharmacokinetic evaluation in beagle dogs. *Drug Dev. Ind. Pharm., 33*, 649–665.

Zheng, W. J., & James, W. (2003). Influence of Eudragit® NE30D blended with Eudragit L30 D-55 on the release of phenylpropanolamine hydrochloride from coated pellets. *Drug Dev. Ind. Pharm., 29*, 357–366.