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Isosorbide-5-mononitrate (5-ISMN) sustained-release pellets prepared by double layer coating for reducing 5-ISMN migration and sublimation

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ABSTRACT

The major aim of this study was to prepare isosorbide-5-mononitrate (5-ISMN) sustained-release pellets and evaluate their stability. The pellets were prepared by extrusion/spheronization, and then the core pellets were coated with ethylcellulose (EC 10cp) and Eudragit®NE30D. Here, EC was used as the subcoating agent while Eudragit®NE30D acted as the outer-coating agent. 5-ISMN sustained-release pellets as a novel drug delivery system contained the immediate-release portion in the outer-coating layer. Unexpectedly, 5-ISMN was found to migrate from the interior of the pellets to the surface forming needle crystals and exhibited the phenomenon of sublimation, which resulted in a tremendous increase in the release rate. Our research showed that the migration and sublimation of the active ingredient was related to the temperature and humidity. Polyvinylpyrrolidone (PVP K30) can affect the precipitation of 5-ISMN by forming a charge transfer complex between the drug and PVP, while hydroxypropyl methyl cellulose (HPMC E5) had no effect, and confirmed the correctness of this view through photographs and IR spectra. In the investigation of the stability, the results showed that there was no sublimation and migration while the pellets stored at 25 °C/60%RH (ambient conditions) and 40 °C/75% RH (stress conditions) during a 6-month period.

1. Introduction

Isosorbide-5-mononitrate (5-ISMN) is one of the major active metabolites of isosorbide dinitrate (ISDN), which is mainly indicated for the treatment of stable and unstable angina pectoris, acute myocardial infarction, and heart failure (Csont and Ferdinandy, 2005; Parker and Parker, 1998). It offers several therapeutic advantages over other organic nitrates, such as good oral absorption, and 5-ISMN was cleared from the body almost exclusively by metabolism and its clearance is about 120 ml/min (Stockis et al., 2002). For a long time, it was used widely in clinical situations for the chronic therapy of coronary artery disease and the prevention of bouts of angina pectoris. These advantages made it a very popular drug in clinical situations (de Belder et al., 1990; Escorsell et al., 1996).

Because the elimination half-life of 5-ISMN is 4–5 h (Stockis et al., 2002), the conventional dosage forms (injection and immediate-release tablets and capsules) required frequent administration (3–4 times/day), which was inconvenient for the patients and often resulted in nitrate tolerance for the nitrates. Some novel preparations of 5-ISMN were produced in United States, which contained almost 30% of the immediate-release form and 70% of the sustained-release form (Bonn, 1988). This allowed the therapeutic effect to be produced in a short time and maintained for a long period while, at the same time, it required administration only once a day and there were no signs of nitrate tolerance. These preparations also provide steady plasma concentrations and improve patient compliance (Nakamura et al., 2006).

5-ISMN is highly soluble and sensitive to moisture, so, the drug undergoes migration when it comes into contact with moisture during the preparation and storage processes, resulting in an increased release rate. In addition, sublimation occurs easily due to the high penetration ability of the drug under a stress temperature and humid environment and, in this article, this was found to be inhibited by adding PVP polymer to the formulation to form a charge transfer complex (Dozal et al., 2000; Hasani and Rezaei, 2006) between PVP and 5-ISMN. The term charge transfer complex (CTC) (Dozal et al., 2000) was introduced by Mulliken to define a new type of adduct to explain the behavior of certain classes of molecules which do not conform to the classical patterns of ionic, covalent, and coordination of hydrogen bonding components. While such adducts largely retain a number of the properties of the components, some changes are apparent, e.g. in solubility and diamagnetic and paramagnetic susceptibility.

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Table 1
The main formulations at different research stages.

Formulation/composition	5-ISMN	MCC (w/w)	PVPK30	HPMCE5 (w/w)	10%HPMC solution (w/w)
1	15%	76%	–	–	9%
2	16%	67%	6%	–	11%
3	15%	65%	13%	–	7%
4	18%	60%	–	10%	12%
5	15%	38%	–	40%	7%

The coating of particles, such as powders, granules, pellets and tablets, to produce controlled-release dosage forms is becoming increasingly popular (Sinchaipanid et al., 2004). Different coating materials (Abbaspour et al., 2005; Siepmann et al., 2008b) can play different roles including control of the release rate, damp, dark, protection from the air in order to increase drug stability. In this study, a double polymer coating was shown to effectively control the drug release rate and improve the stability of the pellets. Polymer EC was selected as the subcoating agent because organic solutions of EC (Kranz and Gutsche, 2009; van der Wel and Adan, 1999) can form even and complete films in order to isolate the moisture and produce a slow-release effect. According to the published literature (Andreuccetti et al., 2009; Bodmeier and Paeratakul, 1994, 1997), diethyl phthalate (DEP) is the most suitable plasticizer for EC compared with other plasticizers, so it was selected as the plasticizer in this research. Eudragit®NE30D aqueous dispersion (Muschert et al., 2009) was chosen as the outer-coating agent since, on the one hand, the pellets coated with EC alone cannot obtain a satisfactory release curves, but it can acquire good results (Fujimori et al., 2005) by the joint use of EC and Eudragit®NE30D while, on the other hand, it is well known that a perfect sustained-release preparation should contain part of the immediate-release form, but the migration appeared when 5-ISMN placed in EC films while, when the drug was embedded in the Eudragit®NE30D coating layer as an immediate-release fraction, the phenomenon of migration was disappeared and it can achieve a therapeutic concentration quickly. The long-term stability testing of the pellets (Muschert et al., 2009; Siepmann et al., 2008a; Wesseling and Bodmeier, 1999) took place under in-house condition (25 °C/60%RH) and stress condition (40 °C/75%RH) (Gil-Alegre et al., 2001).

In this study, 5-ISMN sustained-release capsule was prepared successfully and the preparation had several novelties and advantages: (1) the long-term stability of the preparation was improved by the addition of PVP which inhibited the sublimation phenomena of the 5-ISMN effectively, which could extend the shelf life; (2) because 5-ISMN was a non-ionic drug, the complex reaction would not appear between 5-SIMN and Eudragit®NE30D, in view of this, the immediate-release portion of the preparation can be acquired by adding 5-ISMN to Eudragit®NE30D aqueous dispersion, the benefit of this was that the amount of the immediate-release portion could be controlled accurately, which could avoid the dump release phenomenon induced by single coating material and guarantee the security of the preparation. In addition, 5-ISMN played the role of pore-forming agent and the coating level of Eudragit®NE30D was not high, consequently, the addition of 5-ISMN could not affect the release pattern of the preparation. In contrast, it was not an appropriate selection adding 5-ISMN to EC films for 5-ISMN was insoluble in ethanol, which would change the release pattern of EC films and influence the coating process severely.

2. Materials and methods

2.1. Materials

The materials were obtained from the sources as indicated. Isosorbide-5-mononitrate (5-ISMN; Shandong Keyuan, China), Microcrystalline cellulose PH101 (MCC PH101; Huzhou Zhanwang, China), Eudragit® NE30D (Röhm GmbH Chemische Fabrik, Darmstadt, Germany), Ethylcellucose10cp (EC10cp; Colorcon, Shanghai, China), PVPK30 (Boai Xinkaiyuan, Henan, China), Diethyl phthalate (DEP), HPMCE5 (Huzhou, Zhanwang, China), Granulator (WL350, Wenzhou Pharmacy Equipment Factory, China) 95% alcohol and purified water. All chemicals were reagent grade or higher.

2.2. Preparation of drug-loaded pellets

Pellets were prepared by the extrusion/spheronization technique. Five formulations are listed in Table 1. After mixing 5-ISMN, MCC with sufficient PVP or HPMC, a 10%HPMC aqueous solution was used as the adhesive and added to prepare the wet mass. The mass was extruded into cylindrical strips. At the beginning of spheronization, a low speed was maintained for 2–4 min to cut the long cylindrical mass into 0.5 cm cylindrical strips, and then the rotation speed was increased to 200 rpm for another 30 min. The drug-loaded pellets were collected and dried in the 40 °C oven for 12 h and, finally, the pellets were screened using standard 18–24 mesh sieves to obtain a narrow particle size range.

2.3. Coating of pellets

2.3.1. EC subcoating

Subcoating materials ((1) EC:PVPK30 = 5:1 (w/w); (2) EC:DEP:PVPK30 = 5:1:1 (w/w/w)) were added to 95% (v/v) alcohol with an EC content of 3% (w/w) and stirred overnight prior to coating to make sure the molecular chains of EC expanded completely. PVPK30 was used as a pore-forming agent to obtain a satisfactory release curve. Pellets of 300 g were subcoated in a fluidized bed coater with a bottom spray (FD-MP-01, Powrex, Japan) and the weight gain of EC was 4%. The process parameters were as follows: inlet temperature 30 °C, outlet temperature 25 °C, product temperature 28 ± 2 °C, spray rate 1.5–2 ml/min, atomization pressure 1.2 bar, and nozzle diameter 1 mm. After coating, the pellets were further fluidized for 5 min.

2.3.2. Eudragit® NE30D coating

Eudragit® NE30D is an aqueous polymer dispersion composed of methyl methacrylate and ethyl acrylate monomers in a ratio of 2:1. In this study, Eudragit®NE30D was used on two occasions: (1) Eudragit®NE30D was used to control the drug release rate by its permeability and (2) a portion of isosorbide-5-mononitrate (accounted for 20% of the content of pellets) as the immediate-release fraction was added to the Eudragit®NE30D aqueous dispersion. The process was as follows: Eudragit®NE30D aqueous dispersion was diluted with distilled water to 10% (w/w) based on the dry polymer weight and stirred for 30 min. The subcoated pellets were coated with Eudragit®NE30D and the weight gain was 2%. According to the film formation temperature of Eudragit® NE30D, the temperature was set at 20 °C. After the outer-coating process, pellets were cured at 40 °C for at least 24 h to form an intact film.

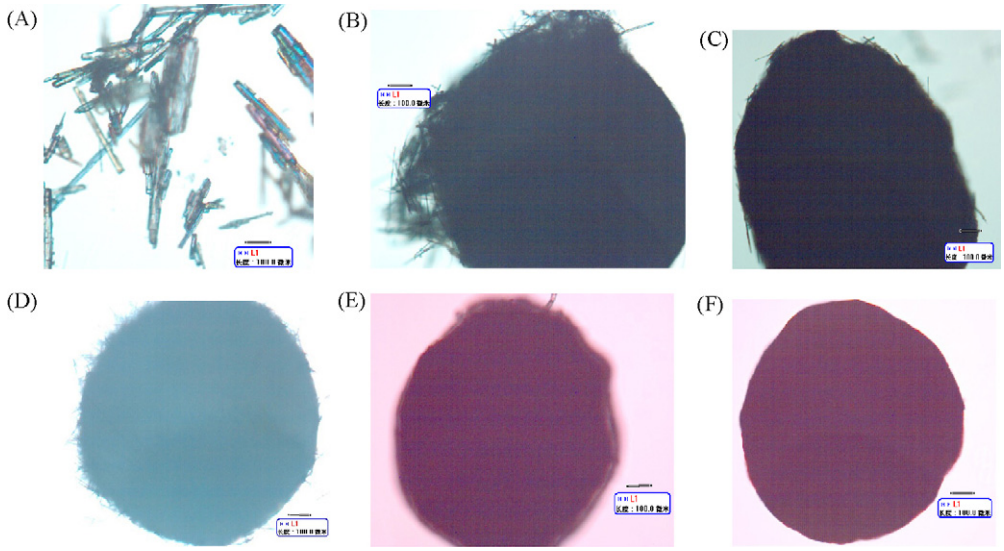

Fig. 1. (A) Microscopy photograph of isosorbide-5-mononitrate; (B) microscopy photograph of pellets without PVP and HPMC (Formulation 1); (C) microscopy photograph of pellets (formulation 4 HPMC:5-ISMN = 60:90); (D) pellets (Formulation 5 HPMC: 5-ISMN = 60:40); (E) pellets (Formulation 2 PVP:5-ISMN=100:240); (F) pellets (Formulation 3 PVP: 5-ISMN = 100:120).

2.4. Dissolution tests

In vitro drug release was determined using the USP XXXIII apparatus 1 (basket) at 50 rpm in 500 ml purified water at 37 ± 0.5 °C. At pre-determined intervals, 5 ml samples were withdrawn and the same volume of purified water was added and the samples were then analyzed by HPLC. The dissolution specification of the pellets was that each capsule contained 40 mg isosorbide-5-mononitrate.

Chromatographic conditions (Huang et al., 2004): Diamonsil C18 column (5 μm, 250 mm × 4.6 mm); mobile phase methanol:water (25:75); flow rate 1 ml/min; UV detector wavelength 210 nm. A plot of the peak areas of 5-ISMN vs. the concentration of 5-ISMN showed a good linear relationship over the range 5.0–200.5 μg/ml with $r = 0.9999$.

2.5. Microscope and scanning electron microscope (SEM) studies

In this study, a microscope (Motic DMBA450, Micro-Optic Industrial Group Co., Ltd) was used to record the change in the pellet surface while the variation in film microstructure was monitored with a scanning electron microscope (SSX-550, Shimadzu, Japan).

2.6. Storage stability

Coated pellets were stored at room temperature (25 °C and 60%RH) and under stress conditions (40 °C and 75%RH). Drug released from the pellets was measured after 1, 2, 3 and 6 months.

3. Results and discussion

3.1. Result of microscopy

The pellets prepared with the above formulations exhibited different properties and appearances. These are shown in Fig. 1.

A common characteristic can be seen from above photographs: there were drug crystal precipitates on the surface of the pellets (Fig. 1B–E) and the crystals were similar to the raw drug crystals (Fig. 1A). It was found that drug crystallization led to a reduction in the drug content and an increased dissolution rate of the drug, and simultaneously affected the long-term stability of the pellets. Thus, it was necessary to add appropriate materials to the formulation in order to inhibit drug migration and recrystallization by certain interactions. In this paper, polymeric HPMC and PVP were added to the later formulations to increase the migration resistance of the drug. However, the pellets which contained polymer exhibited different results. Although there were drug crystals on the surface of the pellets (Fig. 1C–E), the extent of crystallization was not the same in all formulations, and Fig. 1F showed that the pellets which were prepared by formulation 3 had no drug precipitate on the surface. In other words, PVP could slow down the rate of drug outward diffusion and the phenomenon of drug crystallization disappeared if an appropriate ratio of PVP:5-ISMN was used; however, the formulations containing HPMC had no effect irrespective of the amount of HPMC. The reason for this may be as follows:

Isosorbide-5-mononitrate molecules are symmetrical in structure, and the intermolecular force was relatively weak and unstable, and the melting and boiling points were very low and close to each other. So, when the temperature reached a certain value, the intermolecular force would be altered allowing single molecules to be separated. In addition, 5-ISMN is very soluble in water and is sensitive to moisture, so the drug can migrate to the surface of the core pellets accompanied by the evaporation of water. In order to obtain information about the relationship between the drug, PVP and HPMC, infrared scans were recorded for the drugs, polymers and their physical mixture. The spectra were shown in Fig. 2.

The following conclusions can be made from the above spectra. Compared with Fig. 2C and D showed that the intensity of the drug absorption band decreased and many other peaks appeared, while the peak position did not change significantly. The reason for this may be as follows: with an increase of PVP in the formulation, the charge transfer effect increased between PVP and 5-ISMN; this could promote charge equalization, so the polarity of the molecules decreased and the dipole moment was reduced, resulting in a reduction in peak intensity. At the same time, many other peaks appeared, thus novel materials may be formed by special effects instead of hydrogen bonds. Fig. 2F (compared with Fig. 2E) showed that the intensity of the peaks decreased, especially at 800–1400 cm^{-1}, and this may be due to the large and broad absorption bond of HPMC at 800–1400 cm^{-1}. The increase in HPMC disturbed the drug absorption at 800–1400 cm^{-1} and resulted in a reduction in the intensity of the absorption bands. Because the peak position did not change and no novel peaks appeared, it can

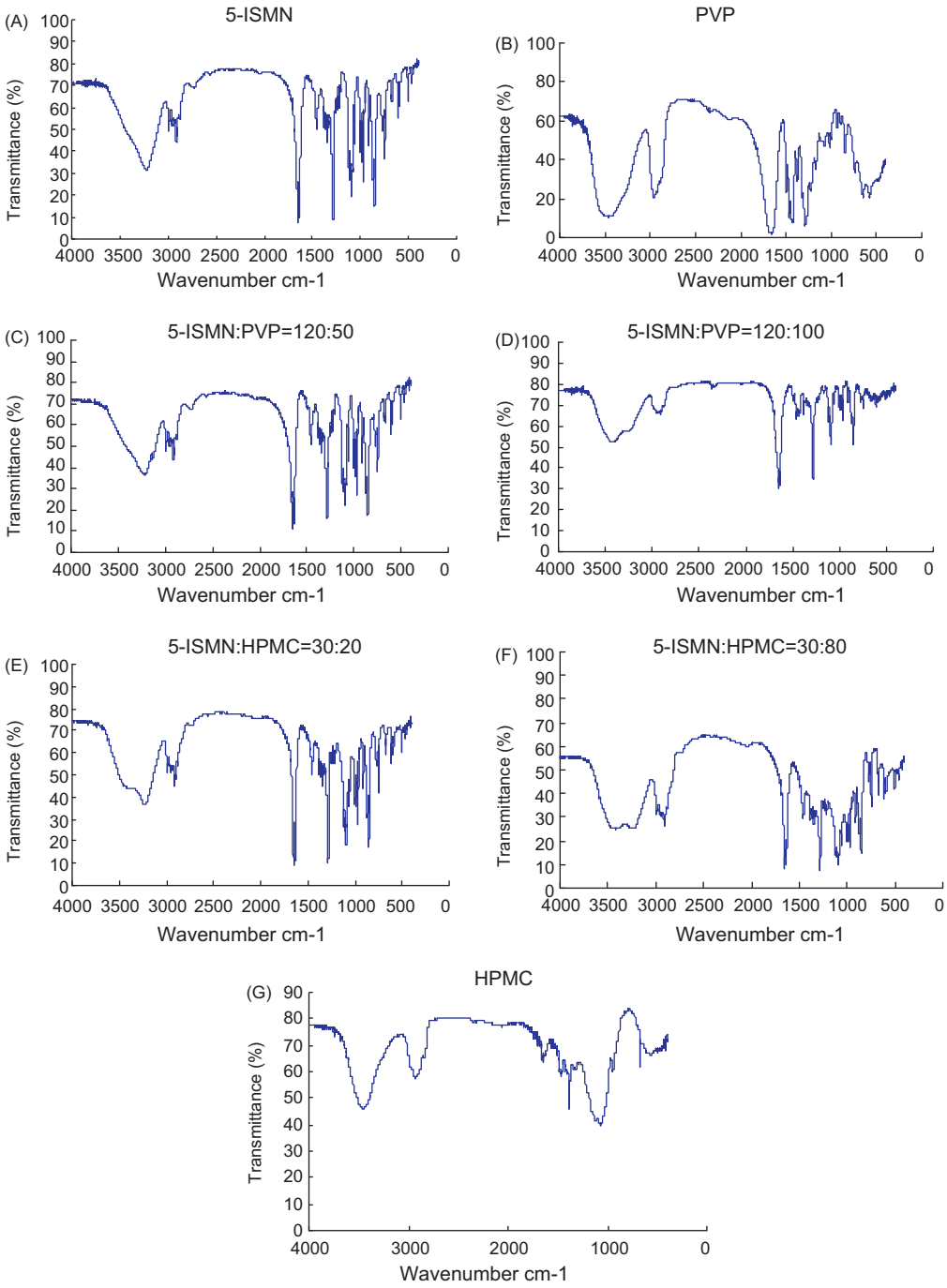

Fig. 2. (A) Infrared absorption spectrum of 5-ISMN; (B) infrared absorption spectrum of PVP; (C) infrared absorption spectrum of 5-ISMN:PVP = 120:50; (D) infrared absorption spectrum of 5-ISMN:PVP = 120:100; (E) infrared absorption spectrum of 5-ISMN:HPMC = 30:20; (F) infrared absorption spectrum of 5-ISMN:HPMC = 30:80; (G) infrared absorption spectrum of HPMC.

be concluded that there was no interaction between HPMC and 5-ISMN. To sum up, PVP can inhibit the precipitation of 5-ISMN, and a charge transfer complex (Hasani and Rezaei, 2006; Matos et al., 1999) between the drug and PVP may be formed. According to Mulliken's charge transfer theory, if there is a difference in electrical properties between two molecules, the charge transfer effect would appear from multi-electron molecules to electron-deficient molecules and generate a charge transfer force. Therefore, this complex was called a charge transfer complex because of this intermolecular force.

In this paper, PVP molecules are in the form of a linear polymer, the main chain of polyethylene is close to the pyrrolidone ring in the PVP structure and the polymer surface is covered with the main chain and the methylene group located on the pyrrolidone ring (Kreft et al., 1999). So, there were van der Waals forces and hydrophobic interactions with other large molecular weight compounds. There were also hydrogen bonds between PVP and other molecules containing hydroxyl groups due to the large number of carbonyl groups on the pyrrolidone rings. Because each pyrrole ring contained a tertiary amine N which absorbed a small amount of hydrogen ions, PVP with a positive charge was formed and interacted with other compounds having a negative charge. These structural features confer some special effects on PVP which are not present in HPMC, so PVP has a weaker ability to bind electrons

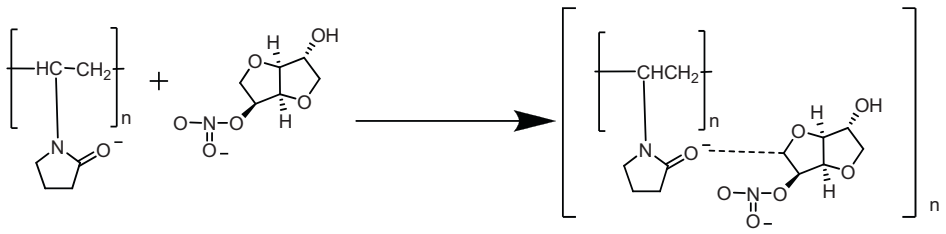

Fig. 3. Charge transfer complex diagrammatic sketch between 5-ISMN and PVP.

which make it a typical n-donor with a lone pair of electrons. However, the hydroxyl group of 5-ISMN was replaced by a nitro group which is strongly electrophilic so that its ring system with oxygen atoms could produce hyperconjugation between adjacent αC–H bonds. The effects described result in the 5-ISMN ring system being in an electron-deficient state. So, when the PVP solution and drug interact, there is a big difference in the charge, which results in electron transfer between PVP and isosorbide-5-mononitrate. Charge transfer forces are created between the two different molecules, and then stable molecular complexes are formed which effectively reduce drug migration and recrystallization. The IR spectra above also show that a charge transfer complex was formed between PVP and the 5-ISMN ring system, rather than between PVP and the nitro group which was connected to the 5-ISMN rings. The infrared spectrum of the nitro group had two strong absorption bands which were a symmetric stretching vibration and an asymmetric stretching vibration, respectively. The former was about 1370 cm^{-1} and the latter was about 1560 cm^{-1}, and these can be seen clearly in spectrum above. Meanwhile, the IR spectrum of 5-ISMN mixed with other polymers had a characteristic nitro absorption peak regardless whether PVP or HPMC was used; however, the IR spectra of polymers changed, especially in the case of PVP. The formation process of this charge transfer complex is shown in Fig. 3.

The migration of 5-ISMN led to a marked increase in the drug release rate. This problem can be solved by the addition of PVP, but, due to the high viscosity of PVP, too much PVP in the formulation would result in the extrusion/spheronization process becoming difficult to carry out and the morphology of the pellets would have an abnormal shape instead of round form which would have an adverse effects on the subsequent coating process. To avoid this, the formulation was optimized with the 5-ISMN:PVP = 120:100.

The migration phenomenon of 5-ISMN was not appear when the drug embedded in the Eudragit® NE30D layers.

3.2. Drug release

3.2.1. Influence of the EC subcoating

5-ISMN was sensitive to water which prompted it to migrate, while the EC alcohol solution could prevent it from coming into contact with water. During the EC coating, with the evaporation of alcohol, EC forms a uniform and continuous film on the surface of the pellets. In order to investigate the effect of EC subcoating on the release profile, the pellets were obtained with different coating weight gains of EC and different quantities of PVP with a fixed amount of EC, and the drug release curves are shown in Fig. 4.

As shown in Fig. 4A, the drug release rate was reduced steadily with the increasing of EC. However, in the case of the pellets coated only with EC, it was difficult to achieve a satisfactory release profile for 5-ISMN. When the weight gain was 2%, it was not possible to control the prophase release because the EC film was so thin that the tortuosity and equitability were insufficient. When the EC coating level was high, the prophase release was satisfactory, but the 5-ISMN in the pellets was not released completely after 8 h. This might be due to the instability of the EC film which allowed film repolymerization and resulted in extension of the diffusion channels (Kranz and Gutsche, 2009).

In this study, PVP was used as a pore-forming agent because of its water solubility. Thus, different amounts in the EC film can change the release rate as shown in Fig. 4B. There was a positive relationship between the amount of PVP and the release rate. When the ratio of PVP:EC was 1:6 or 1:5, the drug release rate was acceptable, but the PVP had a higher viscosity which had a negative impact on the coating process. If the amount of PVP was reduced, the viscosity was also reduced, but the release curve was not satisfactory. Thus, the pellets which were subcoated with EC (EC:PVP = 6:1, containing 20%DEP) with a weight gain of 4% at a concentration of 3% (v/v) in alcohol solution were selected for further study.

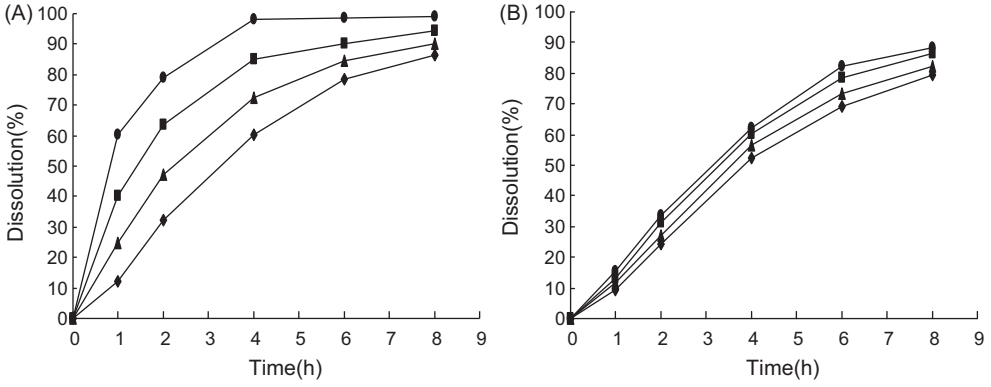

Fig. 4. (A) Effect of the subcoating level of EC (3% alcohol solution and contain 20% DEP) on the drug release of pellets prepared by Formulation 3. (●) 1% EC coating; (■) 2% EC coating; (▲) 3% EC coating; (♦) 4% EC coating. (B) Effect of the amounts of PVP in EC (weight gain 4%) films on the drug release of pellets prepared by Formulation 3. (●) EC:PVP = 4:1; (■) EC:PVP = 5:1; (▲) EC:PVP = 6:1; (♦) EC:PVP = 7:1.

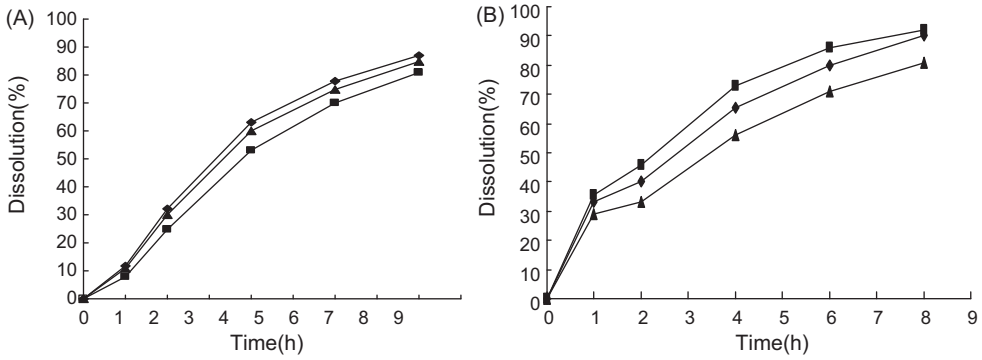

Fig. 5. (A) Effect of Eudragit® NE30D coating (without 5-ISMN) on the drug release of pellets prepared by Formulation 3 with 4% EC subcoating (contains 20% DEP), (♦) 1% Eudragit®NE30D coating; (▲) 2% Eudragit®NE30D coating; (■) 3% Eudragit®NE30D coating. (B) Effect of Eudragit® NE30D coating (contain 5-ISMN which accounted for 20% of content of the pellets) on the drug release of pellets prepared by Formulation 3 with 4% EC subcoating (contains 20% DEP). (■) 1% Eudragit®NE30D coating; (♦) 2% Eudragit®NE30D coating; (▲) 3% Eudragit®NE30D coating;

3.2.2. Influence of the outer-coating

Eudragit® NE30D is an aqueous dispersion of a neutral copolymer and its permeability is independent of the pH, and it has a low viscosity and high dry polymer content. Here, Eudragit®NE30D had two key effects: (1) combination with EC to control the drug release rate and exhibiting a wide range of drug release patterns; (2) it also serves as a vehicle for immediate release in the formulation (the amount of 5-ISMN in Eudragit®NE30D accounts for 20% of the pellet content). The 4% EC subcoated pellets were coated with Eudragit®NE30D at levels of 1%, 2% and 3%, and their release profiles are shown in Fig. 5.

As shown in Fig. 5A, Eudragit®NE30D controlled the release rate perfectly by combination with EC. However, different coating levels of Eudragit®NE30D produced different results because of the permeability release mechanism. When the coating weight gain of Eudragit®NE30D was 1%, there was no difference in release rate for pellets subcoated with only 4% EC. On increasing the coating weight, the release curve became normal as expected. Therefore, when the coating level of Eudragit®NE30D was low, it was mainly used to adjust the prophase release of pellets and had no effect on anaphase release. However, when the Eudragit®NE30D coating level increased, the anaphase release could also be controlled. This phenomenon could be attributed to the release mechanism of Eudragit®NE30D. It was insoluble in water, but it had permeability similar to that of the gel through the pores and the curve of diffusion to control the drug release, and all these were directly related to the coating level which guaranteed the formation of a complete film. Thus, Eudragit®NE30D used as the outer-coating agent could compensate for the disadvantages of EC and produce good results. In addition, Fig. 5B shows that the release curve had a clear protruding section at 1 h, and the main reason was that Eudragit®NE30D aqueous dispersion contained 20% of 5-ISMN which acted as the immediate-release part, for the fraction of the drug embedded in the Eudragit®NE30D layer and it acted as a pore-forming agent due to the water-soluble nature of 5-ISMN. At the same time, there were no migration and sublimation phenomena appeared for 5-ISMN contained in the Eudragit®NE30D layers, the reason may be due to colloidal nature and polymer properties of the Eudragit®NE30D, so some interaction may be existed between Eudragit®NE30D and the 5-ISMN which can improve the stability of the drugs.

3.3. Storage stability

Isosorbide-5-mononitrate sustained-release pellets with a good release profile were stored under stress conditions (40 °C/75%RH) and under ambient conditions (25 ± 2 °C/60%RH).

The drug release patterns of the pellets were determined at 1, 2, 3 and 6 months and the release profiles are shown in Fig. 6.

As can be seen in Fig. 6B, the drug release rate decreased to some extent, but the change was only minor. This may be attributed to the film-forming mechanism of the Eudragit®NE30D layers. It is well known that the curing step is essential for aqueous dispersion coating, which guarantees formation of a complete film. However, the films could undergo re-aggregation (Siepmann et al., 2008a) when the pellets stored at 40 °C/75%RH, clearly indicating that humidity was the main driving force for further polymer coalescence leading

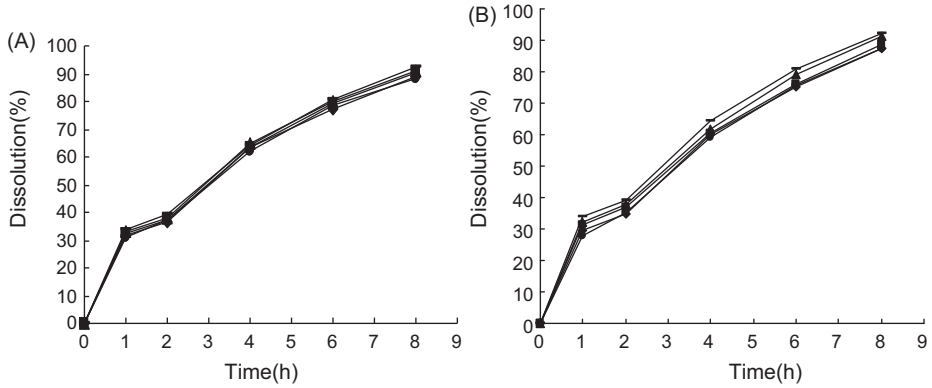

Fig. 6. (A) The drug release of pellets with 4% EC (contain 20% DEP) and 2% Eudragit®NE30D coatings (contain 5-ISMN which accounted for 20% of content of the pellets) stored at 25 °C/60%RH. (–) 0 month; (▲) 1 month; (■) 2 month; (♦) 3 month; (●) 6 month. (B) The drug release of pellets with 4% EC (contain 20% DEP) and 2% Eudragit®NE30D coatings (contain 5-ISMN which accounted for 20% of content of the pellets) stored at 40 °C/75%RH. (–) 0 month; (▲) 1 month; (■) 2 months; (♦) 3 months; (●) 6 months.

to reduced drug release rates (Kranz and Gutsche, 2009). In contrast, following storage at room temperature (25 °C/60%RH), owing to these gentle conditions, the change in drug release was insignificant as shown in Fig. 6A, and the trend was in accord with the release of pellets stored at 40 °C/75%RH. In addition, the coating level of Eudragit®NE30D in this study was not very high, so the re-aggregation effect should not be too great.

Accordingly the long-term stability of the 5-ISMN sustained-release pellets met the requirement specifications after 6 months' storage.

4. Conclusion

Isosorbide-5-mononitrate sustained-released pellets were successfully prepared by double layer coating. The drug sublimation and migration were successfully controlled by adding PVP to the formulation, and explained legitimately the mechanism of drug stability through the microscope photographs and infrared spectra. In order to meet the standards and the requirements of treat, about 20% of 5-ISMN which acted as the immediate-release portion was embedded in the Eudragit®NE30D layers, it was found that it had not appear the drug crystallization phenomenon, the reason may be due to colloidal nature and polymer properties of the Eudragit®NE30D. The pellets with qualified profiles were stored under stress conditions (40 °C/75%RH) and ambient conditions (25 ± 2 °C/60%RH) and the storage stability was monitored by measuring the drug release rate over 6 months. It found that Eudragit®NE30D layers exhibited a degree of instability. In this study, its re-aggregation slowed down the drug dissolution. This was mainly due to the curing time being too short and, thus, the healing time must be long enough to allow formation of a complete layer in terms of aqueous dispersion. All in all, the migration phenomenon of isosorbide-5-mononitrate was controlled effectively, at the same time, the 5-ISMN sustained-release pellets were prepared successfully, and met the required standard specifications.

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