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Preparation and evaluation of nicotinic acid sustained-release pellets combined with immediate release simvastatin

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ABSTRACT

This study was performed to prepare high-dose nicotinic acid (NA) loaded sustained-release pellets coated with double polymer and simvastatin (SIM). The uncoated pellets were prepared by extrusion–spheronization and the double ethylcellucose (EC) films were coated in a bottom-spray fluidized bed coater. SIM was milled by wet grinding and then the milled suspension was layered on the coated pellets. Results showed that coated with 1.5% subcoating and 1% outer coating composed of EC and polyvinyl pyrrolidone K30 (PVP_{K30}) in ratios of 5:1 and 2:1, NA release behavior was very similar to the reference (NER/S; SIMCOR, Abbott) in different media. And SIM was delivered more rapidly than that of the reference, while the SIM layer had no influence on NA release. During 6-month storage at 40 °C/75% RH, the two drugs exhibited stable dissolution behavior. It was observed that the content uniformity of SIM was provided by the present preparation and SIM was stable if adding light magnesium oxide in the grinding procedure. Results indicated it was possible to prepare high-dose sustained-release NA pellets combined with little-dose immediate release SIM by spraying double EC polymer and SIM milled suspension on NA pellets in a bottom-spray fluidized bed coater, respectively.

1. Introduction

NA is a nonhygroscopic white crystalline, highly water soluble drug. It is a very most potent lipid-altering agent for increasing high-density lipoprotein (HDL) cholesterol levels. NA also lowers triglyceride (TG) levels, lowers low-density lipoprotein (LDL) cholesterol levels, and improves lipoprotein particle size and subclass distribution. The major adverse event (AE) of NA is flushing, whereas slow-release NA causes less flushing than immediate release (IR) (McKenney, 2004; Abbott Laboratories, 2007; Meyers et al., 2004).

SIM is also a nonhygroscopic white crystalline powder and poorly water soluble. SIM is widely used, effectively lowers LDL-C levels, has a favorable safety profile, and has been shown to decrease total mortality risk by reducing coronary heart disease (CHD) deaths, myocardial infarction and stroke risk, and coronary with no coronary revascularization (Ward et al., 2007; Ansell, 2005; Birjmohun et al., 2005).

SIM plus NA provides additional clinically relevant improvements in multiple lipid parameters and it is safe and well tolerated in patients with or without diabetes mellitus (PhD, 2004; Ballantyne et al., 2008; Abbott Laboratories, 2008). A proprietary NA extended-release (ER) core (Niaspan, Abbott, Weston, FL, USA) coated with SIM (NER/S; SIMCOR, Abbott) has recently been developed as a single tablet. NA was the sustained-release part while SIM exhibited immediate release. SIMCOR was the reference used in the present trial.

In the present study NA was prepared by extrusion and spheronization and coated by double EC to achieve sustained release and SIM was grinded with magnesium oxide to provide immediate release.

Coated pellets are frequently used for oral sustained drug delivery. Compared with coated tablets and capsules, they avoid the all-or nothing effect of single unit dosage forms and provide less variable transit times, together with a facilitated distribution of the administered drug dose within the gastrointestinal tract (GIT). Compared with controlled release matrix pellets and mini-tablets, higher drug loadings can generally be achieved (Banker, 1966).

In this study EC and Eudragit® NE30D were used as the coating agent for sustained release of NA, respectively. In the latter case, long-term stability might be difficult to achieve, in particular, upon storage under stress conditions (Muschert et al., 2009). EC organic solutions produce a film immediately with a smooth appearance and require no curing. Since NA is a highly water soluble drug, it is more stable and expected to avoid drug migration by lowing drug solubility in the organic coating solvent.

Immediate released SIM could be granulated and blended with NA pellets or grinded feeding before and then layered on the coated pellets to prepare compound pellets. The first program

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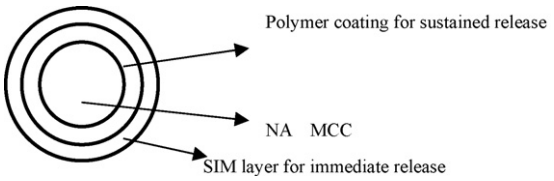

Fig. 1. Schematic diagram of the compound pellets.

was not feasible because of the huge difference in the doses of the two drugs. So, the latter approach was adopted. Fig. 1 shows a schematic diagram of the compound pellets.

2. Materials

The following materials were used: nicotinic acid (Zhongrui, Tianjin, China), Simvastatin (Dabei, Jiangxi, China), microcrystalline cellulose PH101 (MCC PH101; Huzhou Zhanwang, ZheJiang, China), hydroxypropylmethyl cellulose E5 (HPMCE5) (Huzhou Zhanwang, ZheJiang, China), ethylcellucose 10cp (EC10cp; Colorcon, Shanghai, China), polyvinyl pyrrolidone K30 (PVP_{K30}) (Boai Xinkaiyuan, Henan, China), Eudragit® NE30D (Röhm GmbH Chemische Fabrik, Darmstadt, Germany), light magnesium oxide (Bodi, Tianjin, China).

3. Methods

3.1. Preparation of drug-loaded pellets

3.1.1. Preparation of uncoated pellets

The solid components of each formulation, 83% (w/w) NA, 17% (w/w) MCC, were mixed together using an 80 mesh sieve twice to achieve uniform blending. HPMC E5 aqueous solution (10% (m/v)) used as a binder in all formulations. The wet mass was then passed twice through a single screw extruder (WL350, Wenzhou Pharmacy Equipment Factory, China) with a 1.2 mm screen at 120 rpm. The extrudates were processed in a spheronizer (WL350, Wenzhou Pharmacy Equipment Factory, China) fitted with a cross-hatched plate rotated at 300 rpm for about 12 min. The obtained pellets were dried at 40 °C for 12 h in a conventional hot air oven and sized by passing through an 18–24 mesh sieve for further study.

3.1.2. Preparation of coated pellets with EC

The subcoating and outer coating solution was prepared by adding EC and PVP_{K30} (in ratios of 5:1 and 2:1) to 95% (v/v) alcohol with an EC concentration of 3% (w/v) and stirring overnight prior to coating. The pellets (600 g) were coated in turn in a fluidized bed coater (FD-MP-01, Powrex, Japan) with the following technical parameters: the spray gun pressure was 1.1 bar, the rotation speed of the peristaltic pump was 4.0–4.5 ml/min, and the temperature was 30–35 °C.

3.1.3. Layering of SIM

3.1.3.1. Preparation of wet-milled suspension. About 35 g SIM and 12 g light magnesium oxide were added to 500 ml HPMCE5 (7% (m/v)) aqueous solution to prepare the unmilled suspension. Then the suspensions were grinded in a Basket Dispersing Mill (SMA-0.75, Shanghai, China) at 2000 rpm/min for 30 min and then removed from the container.

3.1.3.2. Layering SIM on NA coated pellets. The wet-milled suspension prepared above was stirred constantly during the spraying procedure. A batch of 600 g pellets, which had been already out-coated with EC, was transferred to the fluidized bed coater (FD-MP-01, Powrex, Japan). The pressure of the spray gun was 1.1 bar, the rotation speed of the peristaltic pump was 4.0–4.5 ml/min, and the temperature was 38–40 °C. The pellets were dried at 40 °C for 12 h in a conventional hot air oven.

3.2. In vitro dissolution testing

3.2.1. NA dissolution experiments

Dissolution testing of the coated pellets was performed using USP31-NF26 Apparatus 1 (basket) at 100 rpm in 900 ml solution (pH 4.5, pH 6.8, 0.1 M HCl and water) at 37 ± 0.5 °C. At different times (1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 24 h), 5 ml samples were withdrawn and replaced by fresh medium. The samples were analyzed at 262 nm (UV-7504, UV/Vis spectrophotometer, Xin Mao Instrument Company, Shanghai, China). The amount of NA in the dissolution flask was limited to 250 mg.

3.2.2. SIM dissolution experiments

The SIM was analyzed by HPLC (as described in Section 3.3) with UV detector at 238 nm. The dissolution test was performed using Apparatus 1 (basket) at 100 rpm in 900 ml buffer solution at 37 ± 0.5 °C. The time intervals were 5, 10, 20, 30, 45 and 60 min. And 10 mg SIM was limited to the dissolution flask.

The dissolution behaviors of SIM (pellets and reference) were also evaluated in media: 0.01 M sodium dihydrogen phosphate (pH 7.0) containing 0.1%, 0.3%, 0.5% SDS and buffer solutions alone at pH 7.0.

3.3. Drug content analysis

Chromatographic conditions for NA determination were as follow: Venusil ABS C18 column (5 μm, 250 mm × 4.6 mm, China); mobile phase: acetonitrile–0.005 M sodium hexanesulfonate water (pH 3.0) (5:95); flow rate 1.0 ml/min; HPLC was equipped with a HITACHI pump L-2130 (Tokyo, Japan) and a HITACHI UV Detector (Tokyo, Japan); UV detector wavelength was 262 nm. A plot of the NA peak areas vs. concentration showed a good linear relationship over the range 4.0–200.0 μg/ml with $r = 0.9998$.

The content of SIM was analyzed according to the US Pharmacopoeia (USP31-NF26) by HPLC. Chromatography was performed on a Hypersil C_{18} column (4.6 mm × 250 mm, America) at room temperature using a mobile phase of acetonitrile–0.025 M sodium dihydrogen phosphate (65:35) at a flow rate of 1 ml/min. The detection wavelength was at 238 nm. The SIM peak area vs. concentration showed a good linear relationship over 4.0–200.0 μg/ml with $r = 0.9999$.

3.4. Detection of the related substances of SIM

The related substances of SIM were measured by HPLC according to USP31-NF26, and the chromatographic conditions were the same with content analysis. 20 μl of sample solution when SIM was about 100 μg/ml was injected into the HPLC as the test solution, and then it was diluted to around 1 μg/ml to be as the reference solution. And over a range of 0.4–4.0 μg/ml the SIM peak area vs. concentration still showed a good linear relationship, $r = 0.9998$.

3.5. Scanning electron microscopy (SEM)

A scanning electron microscope (SSX-550, Shimadzu, Japan) was used to examine the surface and cross-section of the pellets after applying a gold coating.

3.6. Stability testing

After 5 and 10 days storage under the stress conditions (elevated temperature and relative humidity) of 60 °C and 25 °C/90 ± 5% RH,

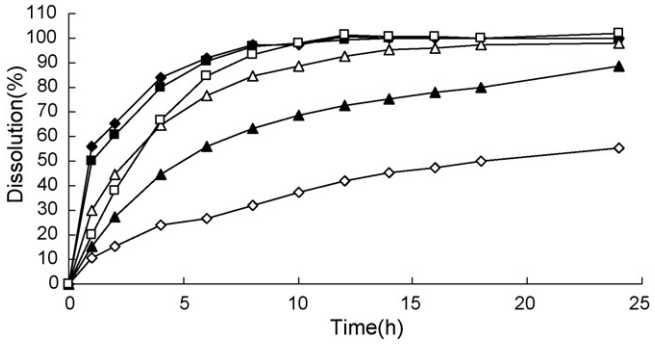

Fig. 2. NA dissolution of pellets coated with different EC levels and different ratios between EC and PVP_{K30} (0.1 M HCl), (■) 2% EC (EC:PVP_{K30} = 3:1); (▲) 2% EC (EC:PVP_{K30} = 4:1); (♦) 1% EC (EC:PVP_{K30} = 3:1); (◊) 2.5% EC (EC:PVP_{K30} = 4:1); (□) 1.5% EC (EC:PVP_{K30} = 4:1); (△) 1.5% EC (EC:PVP_{K30} = 5:1).

the content and related substances of SIM in the compound pellets were analyzed, respectively.

Then the compound pellets were stored at 40 °C/75% RH (LRH-250-Y, Zhujiang, China) and the drug release of the two substances was determined after 1, 2, 3 and 6 months of storage.

4. Results and discussion

4.1. Influence of EC subcoating

Aqueous polymeric dispersions have been extensively used for slow-release film coating of pharmaceutical solid dosage forms. These coating systems have many advantages over organic solvent-based systems with respect to ecological, toxicological and manufacturing safety concerns. However, the major limitation of many aqueous polymeric coating formulations is the risk of premature drug release (permeation). This could be due to an increased permeability of the aqueous film coating or to a high water solubility of the drug (Guo et al., 2002; Bruce et al., 2003). So, a subcoating layer was needed before the outer coating. Stearic acid (hot-melt subcoating) and EC organic solutions can both be used as subcoatings for sustained-release pellets. Hot-melt subcoating is obtained by a coating pan and corrosion was the dissolution mechanism while EC subcoating was carried out using a fluidized bed coater and the drug diffuses from the port hole formed by pore-forming agent (Ng et al., 2010; Lecomte et al., 2004; Shen et al., 1996). However, the corrosion products formed could force the coating to crack and/or delaminate and there could be dumping in the drug dissolution during long-term storage (Ng et al., 2010; Lecomte et al., 2004). So, in our present study EC organic solutions were chosen for subcoating.

Drug-loaded pellets were prepared and coated with EC at different coating levels and different ratios of EC and PVP_{K30}. PVP_{K30} in EC subcoating solution acts as a pore-forming agent and, to some extent, a plasticizer (Shen et al., 1996). The release profiles are illustrated in Fig. 2. It can be seen that the drug release from polymer coated pellets depended on both the coating levels and ratios of EC and PVP_{K30}. And when PVP_{K30}:EC was exceed 1:3, burst occurred. It can be seen in Fig. 2 that a satisfactory drug release profile could not be obtained when the pellets were coated with EC alone. Consequently, the outer coating was needed to deal with the drug release.

4.2. Influence of the outer coating

In the current experiment, EC was served as an outer coating film. The dissolution behavior of a 1% EC outer coating with various ratios of EC and PVP_{K30} is illustrated in Fig. 3. A satisfactory

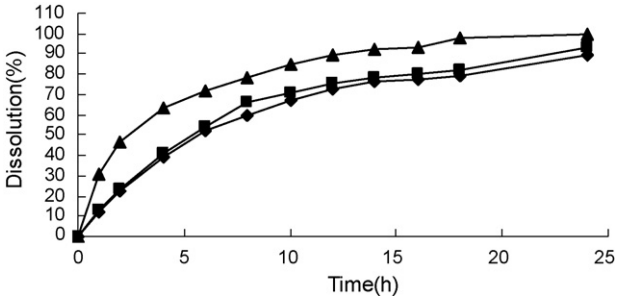

Fig. 3. NA dissolution of pellets coated 1.5% EC subcoating with the outer coating of different ratios between EC and PVP_{K30} (0.1 M HCl), (▲) 1% EC (EC:PVP_{K30} = 1:1); (■) 1% EC (EC:PVP_{K30} = 2:1); (♦) 1% EC (EC:PVP_{K30} = 3:1).

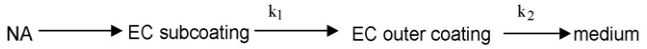

Fig. 4. The schematic diagram of NA diffusion procedure from the coated pellets.

release profile could be obtained with 1.5% EC (EC:PVP_{K30} = 5:1) subcoating plus 1% EC outer coating (EC:PVP_{K30} = 2:1). The release mechanism of the double polymer may be attributed to diffusion through the holes of the two layers of EC polymer. Also, NA needs to step over two layers of film in turn and the diffusion procedure was contiguous just like the continuous reaction (first-order continuous reaction) in the chemical kinetics, shown in Fig. 4. In the process of diffusion, k_1 was determined by both the thickness of the EC subcoating and the ratios of EC and PVP_{K30}, while k_2 was limited only by the ratios of PVP_{K30} and EC, and $k = k_1 \times k_2$ (Frenning et al., 2003; Ozturk et al., 1990).

The regression equation of NA release through the EC subcoating only and the EC double film was $y = 0.39365t^{0.34488}$ and $y = 0.21721t^{0.47701}$ (y: dissolution%, t: time), respectively, so that the release behavior followed a first-order model, with k and k_1 values of 0.345 and 0.477. So, k_2 was calculated to be 0.723 ($k_2 = k/k_1$).

It seemed that, with the EC outer coating, the early release of NA was controlled and a steady delivery was obtained in the later stages (Fig. 3).

Eudragit® NE30D is an aqueous dispersion of a neutral copolymer and the permeability is independent of pH; it does not have any pronounced physiological action and is non-toxic (Knop, 1996; Zheng and James, 2003a,b). Thus, it is suitable for the development of sustained-release oral dosage forms. Satisfactory NA release was obtained of 1.5% EC (EC:PVP = 5:1) subcoated pellets with 1% Eudragit® NE30D. However, the results showed that the drug release was slow when the pellets were stored under stress conditions and at 40 °C/75% RH in Figs. 5 and 6. The reason may

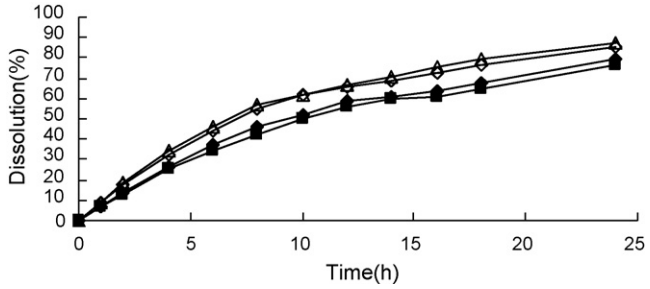

Fig. 5. NA dissolution of pellets coated with 1.5% EC subcoating (EC:PVP_{K30} = 5:1) and 1% Eudragit® NE30D outer coating under stress condition (0.1 M HCl), (▲) 60 °C, 5 days; (■) 60 °C, 10 days; (△) 25 °C/90 ± 5% RH, 5 days; and (◊) 25 °C/90 ± 5% RH, 10 days.

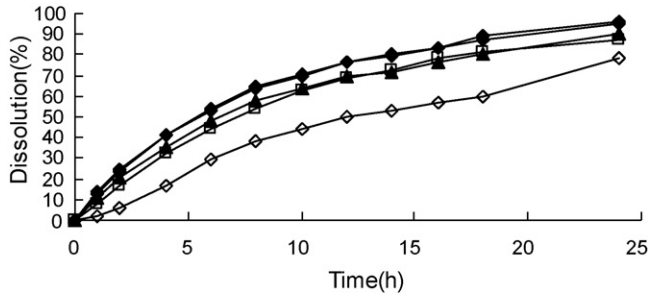

Fig. 6. NA dissolution of pellets coated with 1.5% EC subcoating (EC:PVP_{K30} = 5:1) and 1% Eudragit® NE30D outer coating at 40 °C/75% RH (0.1 M HCl), (♦) zero time; (■) 1 month; (▲) 2 months; (□) 3 months; and (◊) 6 months.

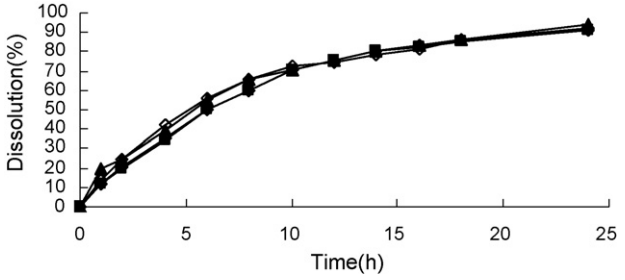

Fig. 7. NA dissolution of pellets coated with EC (EC:PVP_{K30} = 5:1) + EC (EC:PVP_{K30} = 2:1) under stress conditions (0.1 M HCl), (♦) 60 °C, 5 days; (■) 60 °C, 10 days; (▲) 25 °C/90 ± 5% RH, 5 days; and (◊) 25 °C/90 ± 5% RH, 10 days.

be an aging problem (Siepmann et al., 2008; Wu and McGinity, 2000). Eudragit® NE30D was sprayed in a form of polymer dispersion, and it was involved in the further gradual coalescence of the colloidal polymer particles, which resulted in lower release of the drug during storage.

4.3. Stability of NA sustained-release pellets

NA sustained-release pellets coated with double EC films were stored at 60 °C, 25 °C/90 ± 5% RH and 40 °C/75% RH, respectively. The drug dissolution was measured and the dissolution profiles are shown in Figs. 7 and 8.

However, there was no apparent change in the dissolution behavior vs. zero time with double EC film coatings. EC is a good film former and the drug dissolution behavior did not change during the storage (Desai et al., 2006). Also, because NA is highly water soluble, so it was more stable and expected to avoid drug migration by lowering the drug solubility in an organic coating solvent.

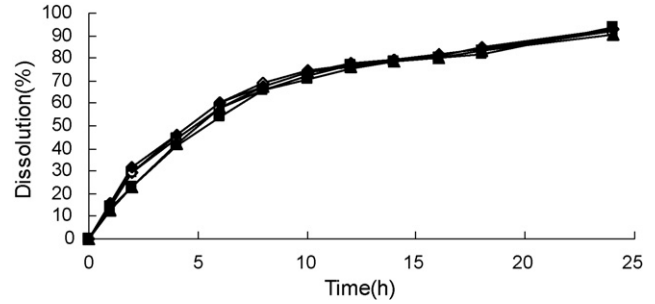

Fig. 8. NA dissolution of pellets coated with 1.5% EC subcoating (EC:PVP_{K30} = 5:1) and 1% EC outer coating (EC:PVP_{K30} = 2:1) at 40 °C/75% RH (0.1 M HCl), (♦) zero time; (▲) 1 month; (◊) 2 months; (□) 3 months; and (■) 6 months.

Table 1
Stability of SIM in compound pellets in stress testing.

Condition	Time (d)	Content (%)	Related substances (%)
60 °C	0	99.1	0.87
	5	99.1	0.90
	10	99.2	0.88
25 °C/90 ± 5% RH	5	99.2	0.91
	10	99.1	0.89

4.4. SIM loading process

4.4.1. The stability agent

SIM is easily degraded by hydrolysis and oxidation during storage. It would produce simvastatin acid by breaking the lactone ring under humid conditions or become a dipolymer and polymer following co-polymerization of the interior diene at a high temperature (Yan et al., 2009).

SIM was unstable and, without a stabilizing agent, it would degrade about 30% after 1 month at 40 °C/75% RH and room temperature (25 ± 2 °C). So, a stabilizing agent needs to be added, and light magnesium oxide was chosen in this study. Light magnesium oxide is a multiporous crumbly fine powder and SIM can be parceled inside it during the preparation of wet milling (Wang et al., 2010; Chakrabarti et al., 2002). So SIM is protected from oxygen in the storage. When exposed in the air, light magnesium oxide was easily to generate magnesium hydroxide gradually by absorbing moisture to create a slightly alkaline surroundings, which could be used as the drying agent and to prevent hydrolysis.

The SIM content and related substances were determined after 5 and 10 days in the storage of stress conditions (60 °C and 25 °C/90 ± 5% RH) to investigate the stability effect of light magnesium oxide. The content was almost the same with the zero time, which degraded little. And the related substances also increased nothing compared to zero time (Table 1). It was shown that the formulation was safe and the preparation procedure in the present study was suitable.

4.4.2. Uniformity of the SIM content

In the formula, there was a great disparity between the dose of NA and SIM. As explained before, blending NA pellets and SIM granules were not feasible. So, the milled suspension was layered on the coated pellets using a fluidized bed coater. The SIM content was measured by HPLC (described in Section 3.3) as in the drug content analysis and the average of the content was 99.13% with relative standard deviation = 0.50%, which showed that the SIM content was homogeneous.

4.4.3. Influence of the SIM layer on NA release

Since the softening temperature of EC was 135–155 °C, the temperature of the fluid bed coater could be 38–40 °C which was in favor of the layering process. Fig. 9 shows that the SIM layer had no effect on the release of NA and that indicated the double EC

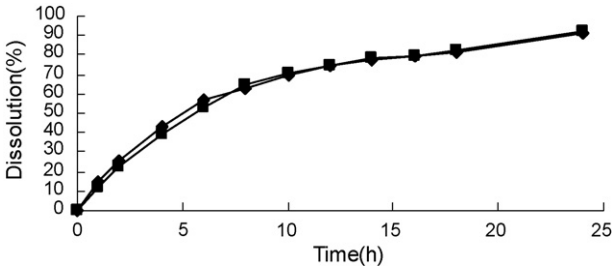

Fig. 9. NA dissolution of pellets coated 1.5% EC (EC:PVP_{K30} = 5:1) subcoating and 1% EC outer coating (EC:PVP_{K30} = 2:1) (0.1 M HCl); (♦) layering SIM; and (■) without SIM.

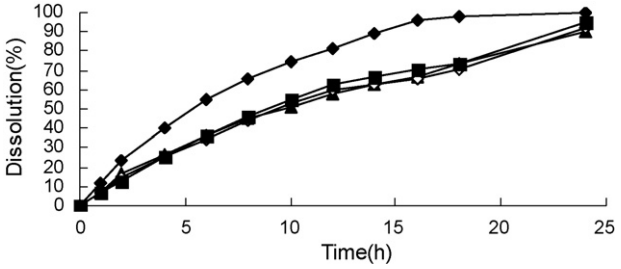

Fig. 10. NA dissolution of SIMCOR in different media: (♦) 0.1 M HCl; (■) water; (▲) pH 4.5; and (◊) pH 6.8.

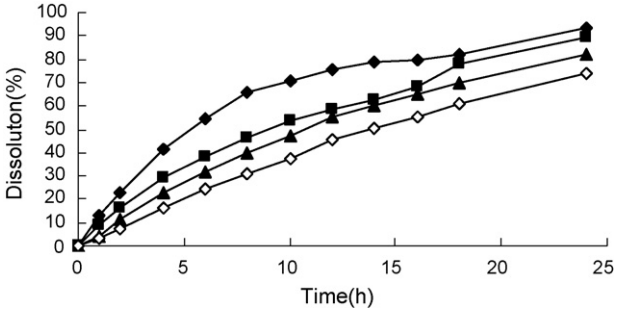

Fig. 11. NA dissolution of compound pellets coated 1.5% EC (EC:PVP_{K30} = 5:1) subcoating and 1% EC outer coating (EC:PVP_{K30} = 2:1) and layering SIM in different media, (♦) 0.1 M HCl; (■) pH 4.5; (▲) pH 6.8; and (◊) water.

films were still complete after spraying SIM on the coated pellets.

4.5. Comparison of dissolution behavior of the compound pellets with SIMCOR

The NA dissolution behavior of the compound pellets and SIMCOR was evaluated in different media. The NA dissolution behavior was essentially similarly after SIM coating in different media mentioned above (pH 4.5, pH 6.8, 0.1 M HCl and water) (Figs. 10 and 11) and the values of $f2$ were 89.63, 77.37, 82.95 and 53.77, respectively.

The SIM dissolution behavior of compound pellets and SIMCOR was also evaluated in different media. In Figs. 12 and 13, it was seen that the SIM was discharged more rapidly than the reference in every medium and delivered completely in 5 min in 0.01 M sodium dihydrogen phosphate (pH 7.0) including 0.3% and 0.5% SDS, respectively. The reason for this may be that the tablets were made by pressing and the SIM released from the interior while the SIM was sprayed on the surface of the coated pellets.

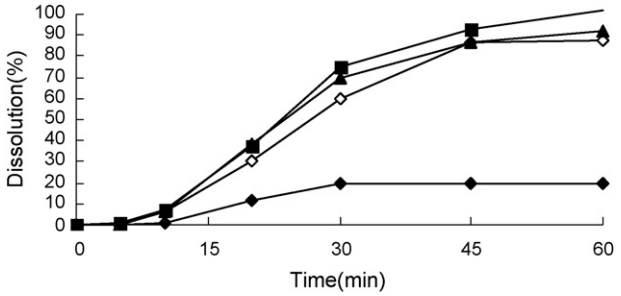

Fig. 12. SIM dissolution of SIMCOR in different media: (♦) pH 7.0; (■) pH 7.0, 0.5% SDS; (▲) pH 7.0, 0.3% SDS; and (◊) pH 7.0, 0.1% SDS.

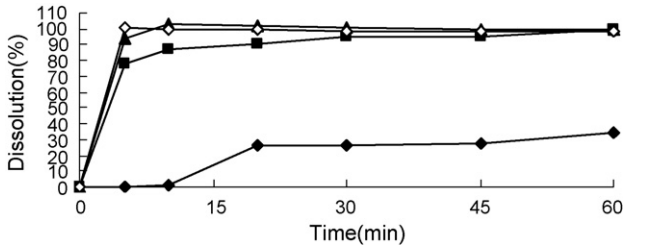

Fig. 13. SIM dissolution of compound pellets coated 1.5% EC (EC:PVP_{K30} = 5:1) subcoating and 1% EC outer coating (EC:PVP_{K30} = 2:1) and layering SIM in different media: (♦) pH 7.0; (■) pH 7.0, 0.1% SDS; (▲) pH 7.0, 0.3% SDS; and (◊) pH 7.0, 0.5% SDS.

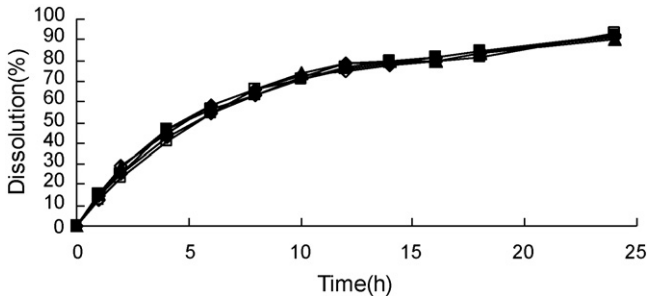

Fig. 14. NA dissolution of compound pellets at 40 °C/75% RH in 0.1 M HCl: (♦) zero time; (■) 1 month; (▲) 2 months; (□) 3 months; and (◊) 6 months.

4.6. Dissolution stability of the compound pellets

After 1, 2, 3 and 6 months of storage at 40 °C/75% RH, the dissolution of the two drugs in the compound pellets was determined. Figs. 14 and 15 shows that the two drugs exhibited stable dissolution behavior.

4.7. Scanning electron microscopy (SEM)

Fig. 16 shows the scanning electron photomicrographs of pellets with a 1.5% subcoating with the two kinds of outer coating layered SIM, which matched the schematic diagram in Fig. 1. The surfaces of the pellets were smooth (Fig. 16A and C), and the SIM layer was uniformly distributed (Fig. 16B and D). This showed that the procedure of layering SIM by the bottom-spray fluidized bed was satisfactory to obtain a content uniformity of SIM. Besides, the immediate release layer did not affect the sustained-release behavior of NA, in which the SIM was present in the porous form, and SIM dissolved completely within 5 min.

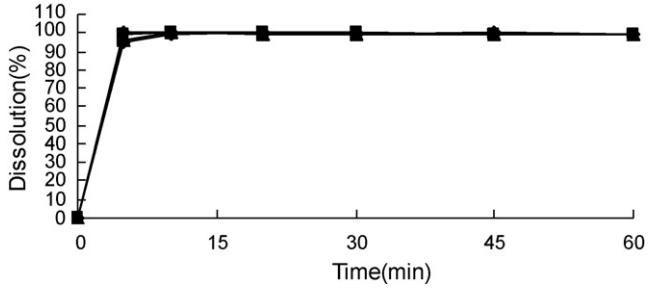

Fig. 15. SIM dissolution of compound pellets at 40 °C/75% RH in pH 7.0, 0.5% SDS buffer solution: (♦) zero time; (■) 1 month; (▲) 2 months; (□) 3 months; and (◊) 6 months.

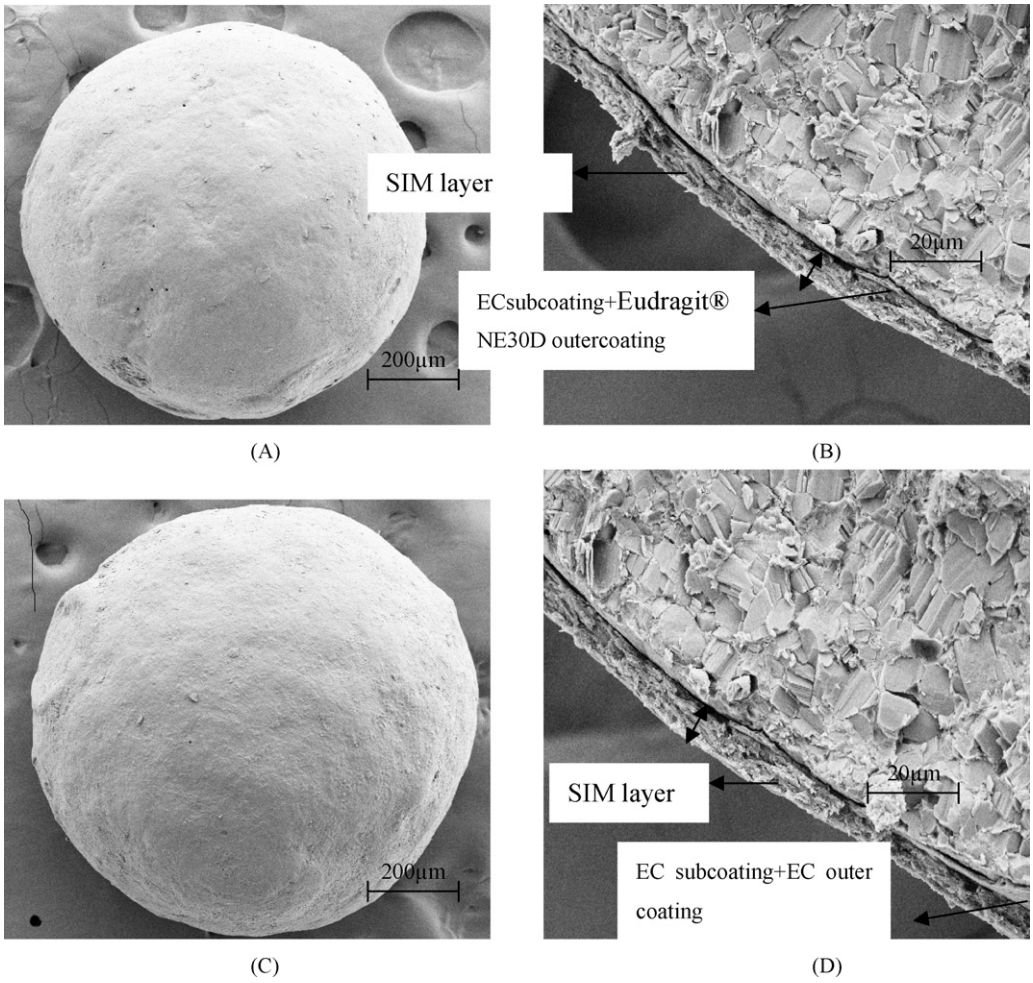

Fig. 16. (A) SEM photograph of a pellet with 1.5% EC (EC:PVP_{K30} = 5:1) subcoating and 1% Eudragit® NE30D outer coating and simvastatin outside; (B) SEM photograph of a cross-sectional view of a pellet with 1.5% EC (EC:PVP_{K30} = 5:1) subcoating and 1% Eudragit® NE30D outer coating and simvastatin outside; (C) SEM photograph of a compound pellet with 1.5% (EC:PVP_{K30} = 5:1) subcoating and 1% EC (EC:PVP_{K30} = 2:1) outer coating and simvastatin outside; (D) SEM photograph of a cross-sectional view of a compound pellet with 1.5% (EC:PVP_{K30} = 5:1) subcoating and 1% EC (EC:PVP_{K30} = 2:1) outer coating and simvastatin outside.

5. Conclusion

In this work, NA sustained-release pellets combined with immediate release SIM was successfully prepared by the double EC polymer and SIM milled suspension layering on the NA pellets in a bottom-spray fluidized bed coater. In the compound pellets, NA dissolution behavior was controlled by double EC coating, and SIM was uniformity in the procedure and stable with the effect of light magnesium oxide.

More significantly, a satisfied method to prepare pellets containing more than one drug had been developed in the fluid bed coater, especially there was a large difference between the doses of the two drugs.

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References

Abbott Laboratories, 2007. Niaspan tablets: niacin extended-release tablets, Available at: http://www.rxabbott.com/pdf/niaspan.pdf.

Abbott Laboratories, 2008. Simvastatin niacin extended-release tablet. Film Coated, 33. DN1744V1-Simcor-ADRChange-clean-041508.

Ansell, B.J., 2005. Rationale for combination therapy with statin drugs in the treatment of dyslipidemia. Curr. Atheroscler. Rep. 7, 29–33.

Ballantyne, C.M., Davidson, M.H., McKenney, J., Keller, L.H., Bajorunas, D.R., Karas, R.H., 2008. Comparison of the efficacy and safety of a combination tablet of niacin extended-release and simvastatin with simvastatin 80mg monotherapy: the SEACOST II (high-dose) study. J. Clin. Lipidol. 2, 79–90.

Banker, G.S., 1966. Film coating theory and practice. J. Pharm. Sci. 55, 81–89.

Wang, B.-H., Wang, Z.-H., Wang, G., Xu, Q., 2010. Preparation and abnormal infrared behavior of highly-dispersed magnesium oxide powders. Henan Chemical Industry. 03, 01-0037.

Birjmohun, R.S., Hutten, B.A., Kastelein, J.J., Stroes, E.S., 2005. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J. Am. Coll. Cardiol. 45, 185–197.

Bruce, L., Diane, Koleng, John, J., McGinity, James, 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.

Chakrabarti, S., Ganguli, D., Chaudhuri, S., Pal, A.K., 2002. Crystalline magnesium oxide films on soda lime glass by sol–gel processing. Mater. Lett. 54, 120–123.

Desai, J., Alexander, K., Riga, A., 2006. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. Int. J. Pharm. 1–2, 115–123.

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

Guo, H.X., Heinämäki, 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.

Knop, K., 1996. Influence of buffer solution composition on drug release from pellets coated with neutral and quaternary acrylic polymers and on swelling of free polymer films. Eur. J. Pharm. Sci. 4, 293–300.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2004. Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques. Pharm. Res. 21, 882–890.

McKenney, J., 2004. New perspectives on the use of niacin in the treatment of lipid disorders. Arch. Intern. Med. 164, 697–705.

Meyers, C.D., Kamanna, V.S., Kashyap, 2004. ML: niacin therapy in atherosclerosis. Curr. Opin. Lipidol. 15, 659–665.

Muschert, Sa., Siepmann, Fa., Leclercq, Bb., Carlin, Bc., Siepmann, Ja, 2009. Prediction of drug release from ethylcellulose coated pellets. J. Control. Release 135, 71–79.

Ng, W.F., Wong, M.H., Cheng, F.T., 2010. Stearic acid coating on magnesium for enhancing corrosion resistance in Hanks' solution. Surf. Coat. Technol. 11, 1823–1830.

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.

PhD., 2004. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). Am. J. Cardiol. 93, 307–312.

Shen, H.-F., Ren, Q., 1996. Applications of polyvinylpyrrolidone in pharmaceutics. Chin. J. Pharm. 12, 26.

Siepmann, F., Muschert, S., Leclercq, B., Carlin, B., Siepmann, J., 2008. How to improve the storage stability of aqueous polymeric film coatings. J. Control. Release 126, 26–33.

Ward, S., Lloyd, J.M., Pandor, A., Holmes, M., Ara, R., Ryan, A., Yeo, W., Payne, N., 2007. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol. Assess. 11, 1–178.

Wu, C., McGinity, J.W., 2000. Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer. Eur. J. Pharm. Biopharm. 50, 277–284.

Li, Y., Zhao, L.-G., Jing, B.-Y., Wang, L., Sun, J., He, Z.-G., 2009. Effect of different excipients on the stability of simvastatin tablets. Chin. J. Pharm. 03, 0101-07.

Zheng, W.J., James, W., 2003a. Influence of Eudragit® NE30D blended with Eudragit L30 D-55 on the release of phenylpropanolamine hydrochloride from coated pellets. Drug Dev. Ind. Pharm., 595–605.

Zheng, W.J., James, W., 2003b. 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.