ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES 9 (2014) 35–41

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Original Research Paper

Solid dispersion in the development of a nimodipine delayed-release tablet formulation

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ARTICLE INFO

Article history:
Received 19 August 2013
Received in revised form
26 September 2013
Accepted 26 November 2013

Keywords:
Nimodipine
Solid dispersion
Delayed-release
Dissolution test

ABSTRACT

Nimodipine (NMD) is a dihydropyridine calcium channel blocker with selectivity for cerebral blood vessels and the major therapeutic indication of NMD is for the prevention and treatment of delayed ischemic neurological disorders and other cerebrovascular disorders, such as stroke which is associated with biological rhythm. This study was mainly designed to solve the drawback of conventional NMD solid dosage form, low bioavailability and limited clinical efficacy, by preparing enteric solid dispersion (SD) and the SD was prepared via melting method. The physical state of the dispersed NMD in the polymer matrix was characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and dissolution studies. Compared with pure drug and physical mixture, the dissolution of NMD-SD was enhanced dramatically (about 80%). Furthermore, in consideration of the biological rhythm of stroke, we first obtained a delayed-release tablet containing NMD-SD by a direct powder compression method. As shown in the dissolution studies, the tablet released less than 10% in the artificial gastric acid in the initial 2 h and released 32.1%, 75%, more than 90% at 4, 10 and 14 h respectively in the artificial intestinal fluid. This investigation has solved the problems of oral solid dosage forms of NMD, and it has the good industry prospect.

1. Introduction

A poorly water-soluble drug often shows insufficient bioavailability due to its poor solubility and low dissolution rate after administration, especially for class II substances according to the Biopharmaceutics Classification System (BCS). This series of drugs possess low solubility but high penetration, and the bioavailability of them can be greatly improved by accelerating the dissolution process of active pharmaceutical ingredient in the gastrointestinal tract. In

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Peer review under responsibility of Shenyang Pharmaceutical University

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http://dx.doi.org/10.1016/j.ajps.2013.11.006

order to increase the dissolution rate of the drug, means of enhancing its specific surface area or solubility can be take into consideration, such as micronization, enhancing the wettability and solid dispersion technology.

SD technology is an available method which can affect both specific surface area and solubility. It makes compounds disperse in carriers or matrixes at solid state and has been widely used in both pre-clinical and clinical formulation development as a successful approach to deliver insoluble compounds [1]. There are many alternatives for the manufacture of SD, such as melting (fusion), melting-solvent, hot-melt extrusion (HME), spray drying, co-evaporation and freeze-drying. Although SD technique has been extensively confirmed to enhance the dissolution characteristics of the sparingly soluble drugs, the practical applicability of the system has remained limited mainly due to the difficulties in manufacturing process, such as poor reproducibility of physicochemical properties, the complexity of dosage form development and less feasibility for scale up of industrialization. Besides, those carriers, frequently used in solid dispersion, also cause problems of aging due to their hygroscopic nature [2]. Therefore, more attempts about searching new carriers or innovative techniques are needed, and they are especially significant for large-scale manufacturing. In this work, a new excipient, hypromellose acetate succinate (HPMCAS), has been explored to serve for SD carrier material, and co-evaporation and melting were chosen as the fabrication methods.

HPMCAS is usually employed as an enteric coating material for enteric or sustained release formulations. But recently, it is also a polymer which can be applied in SD technology as a new carrier or matrix for poorly water-soluble drugs to increase both dissolution rate and solubility. According to different contents of acetyl and succinoyl groups in the polymer, there are three kinds of HPMCAS on the market, i.e. AS-L, AS-M and AS-H. Type L has a low ratio (0.53) of acetyl substitution to succinoyl substitution (A/S ratio), while type M has a medium A/S ratio (0.81), and a high A/S ratio (2.00) is type H. These three types of excipients dissolve at different levels of pH which increase with A/S ratios: Type L dissolves in a medium of pH 5.5 or higher; type M dissolves at pH 6.0 or higher; type H dissolves at pH no less than 6.8. Besides, every type of HPMCAS is available in fine (mean particle size: 5 μm) and granular particle (mean particle size: 1 mm) [3].

In this investigation, we selected nimodipine, a drug belongs to BCS II, as the model drug. Nimodipine (NMD) is a dihydropyridine calcium channel blocker with selectivity for cerebral blood vessels and the major therapeutic indication of NMD is for the prevention and treatment of delayed ischemic neurological disorders and other cerebrovascular disorders, such as stroke which is indicated to have biological rhythm [4]. Biological rhythm may affect normal biological functions such as heart rate, blood pressure, body temperature, blood-plasma concentration and platelet aggregation [5]. The symptoms of many diseases have followed the body's biological rhythm. The attacks and symptoms of illness like asthma attacks, coronary infarction, angina pectoris, stroke, and ventricular tachycardia are circadian-phase dependent [6]. A few researches have been carried on to provide strong evidence that stroke has a higher risk in the early morning h (03:00 a.m. to 06:00 a.m.) and lower risk during the night time period (21:00 p.m. to midnight). It meant that NMD preparation should be modified to achieve an efficient drug level at an optimum time, improving disease therapy, rather than merely maintaining constant drug concentrations. In one word, biological rhythms may be applied to pharmacotherapy by adopting a dosage form that synchronizes drug concentrations to rhythms in disease activity [7–9].

Oral administration of conventional solid dosage form of NMD is associated with certain problems such as frequent dosing (30–60 mg every 4–8 h), varying half-life, fluctuating plasma concentrations, lower bioavailability and limited clinical efficacy, mainly due to the low water solubility of NMD [10]. In view of chronopharmacology in disease treatment, and that the improvement of NMD dissolution rate is a solution to the problems of lower bioavailability and limited clinical efficacy, the objective of this investigation is to prepare a delayed-release tablet, containing NMD enteric SD which can effectively increase the dissolution rate and reduce dosing frequency. Because the delayed-release function of NMD can be realized via the enteric character of SD, the coating process is omitted for simplifying the process. Because there is a lower risk of stroke during the night time period (21:00 p.m. to midnight), and in view of 2 h' retention time in stomach, the patients can take the medicine at 22:00 p.m. The release profile of the delayed-release tablet will be prolonged, as starting to release at 24:00, and cover the high-incidence period of stroke. In addition, all experiments were carried out in a dark room in view of the sensitivity of nimodipine to light.

2. Materials and methods

2.1. *Materials*

Nimodipine (NMD) was obtained from Zhengzhou Ruikang Pharmaceutical Company (Zhengzhou, Henan, China). Hypromellose acetate succinate (HPMCAS) and Hypromellose Phthalate (HPMCP) was purchased from Shin-Etsu Chemical Co., Ltd. (Japan). Polyvinylacetat-Polyvinylpyrrolidon (Kollidon® SR) was supplied by Trademark BASF. Microcrystalline Cellulose (MCC) was obtained from Asahi Kasei Chemicals Corporation (Japan). Eudragit® RS PO was purchased from Degussa (China) Co., Ltd. Polyethylene oxide (PEO, N-12K) was supplied by The Dow Chemical Company (Shanghai, China).

2.2. *Preparation of solid dispersion containing nimodipine (NMD-SD)*

Co-evaporation and melting methods are the two major options of preparing solid dispersion. Through the preliminary experiments, we selected the melting method other than co-evaporation method, because the melting procedure seemed to be more convenient and it involved with no organic solvent during preparation process, which ensured a cost-effective method of production.

All the excipients and drug were firstly screened through 100-mesh sieve and mixed uniformly to obtain the physical mixture, then melted the physical mixture with stir, followed

by cooling and pulverization of the obtained product. As the last step, the SD powder was screened through 100-mesh sieve. In Table 1, from SD_0 to SD_5, six types of HPMCAS were respectively used to prepare solid dispersions with the condition that the ratio of HPMCAS to NMD is 3:1. To investigate whether the combined carriers were better than the single carrier for improving dissolution of poorly water-soluble drug, we had chosen HP-55, HPMCAS as the combined carriers and HPMCAS as the single carrier. The formulations were summarized in Table 1 (SD_6 and SD_{11}). A further study for confirming the optimal ratio of NMD to carrier with the selected type of HPMCAS was also performed, and the relative formulations, from SD_7 to SD_{11}, were listed in Table 1.

2.3. Preparation of delayed-release tablets

Here, a delayed-release tablet means the enteric tablet, an enteric tablet should meet the characteristic that the drug doesn't release or scarcely release in the gastric fluid and releases completely in the intestinal fluid. Accurate amount of solid dispersion containing 60 mg of NMD, a certain amount of Kollidon® SR, Microcrystalline Cellulose (MCC), Eudragit® RS PO or Polyethylene oxide (PEO) were weighed and mixed together. The formulations are summarized in Table 2. A single-punch press (TDP-5, Shanghai Tianfan Pharmaceutical Machine Factory, Shanghai, China) equipped with a 10 mm diameter concave-faced punch and die set was used in the process of compressing tablets.

2.4. Physical characterization of solid dispersion

2.4.1. Differential scanning calorimetry (DSC)

The DSC patterns were carried out using a Thermal Anacyzer-60WS, Differential Scanning Calorimeter-60 (Shimadzu, Japan). A sample of 10 mg was placed in perforated aluminum pans and scanned through a temperature range of 30–180 °C at a heating rate of 10 °C/min. The samples were pure NMD, HPMCAS, SD, the physical mixture of NMD and HPMCAS.

2.4.2. Powder X-ray diffraction (PXRD)

PXRD was performed to evaluate the physical character of NMD in the samples using an XRD^2 micro-diffractometer (BRUKER-D8 DISCOVER, Germany). The patterns were recorded on a quartz plate at a tube voltage of 56 kV and a current of 182 mA applying a scan rate of 2°/min in the angular range of 0–180° 2θ.

Table 1 – Formulations of SD containing NMD.

Formulation no.	NMD:carrier	Type of carrier
SD_0	1:3	HPMCAS-LF
SD_1	1:3	HPMCAS-LG
SD_2	1:3	HPMCAS-MF
SD_3	1:3	HPMCAS-MG
SD_4	1:3	HPMCAS-HF
SD_5	1:3	HPMCAS-HG
SD_6	1:5	HPMCAS-LF:HP-55 = 3:2
SD_7	1:1	HPMCAS-LF
SD_8	1:2	HPMCAS-LF
SD_9	1:3	HPMCAS-LF
SD_{10}	1:4	HPMCAS-LF
SD_{11}	1:5	HPMCAS-LF

Table 2 – Formulations of NMD delayed-release tablets.

No.	Kollidon® SR (mg)	MCC (mg)	Eudragit® RS PO (mg)	PEO (mg)
Formulation 1	40	60	–	80
Formulation 2	40	–	60	80
Formulation 3	40	20	20	80
Formulation 4	100	–	–	80
Formulation 5	80	100	–	–

2.5. Dissolution studies

The release profiles of solid dispersion and delayed-release tablets were assessed using in vitro dissolution devices. Dissolution studies were conducted according to USP34–NF29 apparatus 2 (paddle method) at 37 °C ± 0.5 °C and 100 rpm. Appropriate amount of SD, physical mixture or the pure drug were precisely weighted. Furthermore, the dissolution tests of NMD-SD were respectively performed in pH 1.2 and pH 6.8 media for 2 h. A 5 ml sample was withdrawn at 0.5, 1 and 2 h from the 900 ml pH 1.2 media. In the pH 6.8 buffer solution, a 5 ml sample was taken from the 900 ml dissolution media at 5, 15, 25, 35, 45, 60 and 120 min. For the delayed-release tablets, the dissolution studies were performed under sink condition by adding 0.5% sodium dodecyl sulfate (SDS) into the dissolution media. The dissolution media were 750 ml pH 1.2 media (2.0 g NaCl, 7.0 ml HCL and H_2O) for the first 2 h, followed by pH 6.8 phosphate buffer solution (addition of 250 ml of 0.2 M sodium triphosphate buffer) for the next 12 h. A 5 ml sample was withdrawn for every 2 h and each sample was passed through 0.45 μm filter, and the drug content of it was determined by UV spectrophotometer at 238 nm for SD or 356 nm for tablets. Also a 5 ml fresh medium was added after each sampling. The cumulative percentages of the drug dissolved from the SD and the delayed-release tablets were calculated ($n = 3$, mean ± SD).

3. Results and discussion

3.1. Physical characterization of solid dispersion

In this part, results of DSC and PXRD were adopted to identify the physical state of the drug in SD and its physical mixture. Among the NMD-SD formulations, SD_8 and its physical mixture were tested, also the pure NMD and the excipient HPMCAS were studied.

3.1.1. Powder X-ray diffraction (PXRD)

The results of PXRD were shown in Fig. 1. For pure drug and corresponding physical mixture of SD_8, a lot of diffraction rings which represented information of NMD crystalline diffraction peaks were detected in partial region. However, no obvious rings were observed in SD_8 pattern and HPMCAS pattern at the corresponding position, i.e. no crystalline NMD was detected [11]. Comparing Fig. 1a and c, difference could be found that Fig. 1c still showed the same diffraction rings as

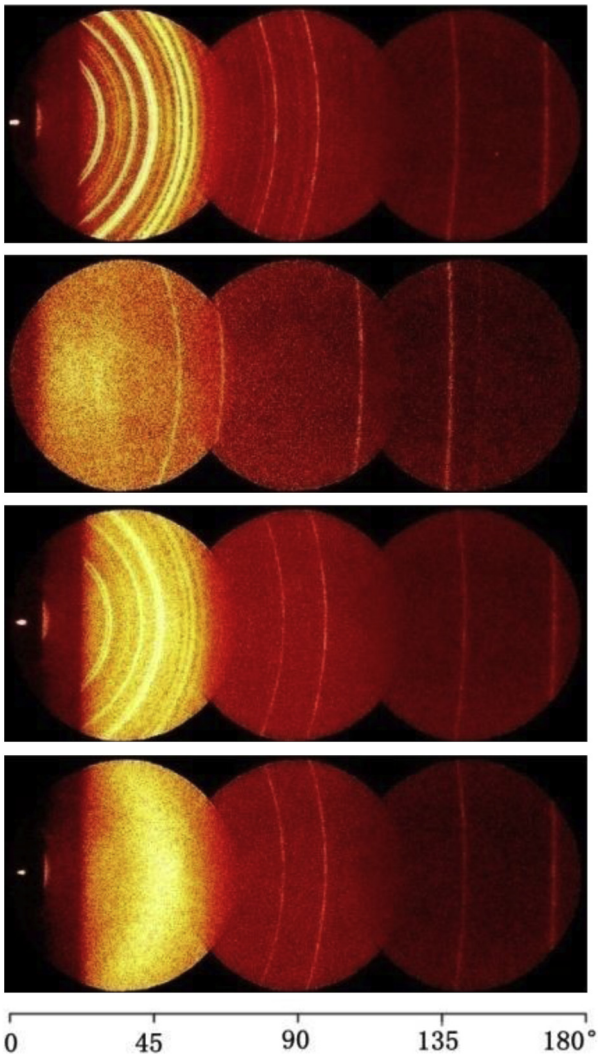

Fig. 1 – Powder X-ray diffraction (PXRD) diagrams. From top to bottom: (1) pure NMD; (2) HPMCAS-LF; (3) physical mixture of NMD and HPMCAS-LF (1:2); (4) SD_8

Fig. 1a, but the diffraction rings of Fig. 1c were weaker than Fig. 1a. So it indicated that the crystalline form of NMD still existed in the physical mixture. In addition, Fig. 1d had no diffraction ring. The difference between Fig. 1a and d revealed that the drug was in an amorphous state in SD_8.

3.1.2. *Differential scanning calorimetry (DSC)*

The limit of detection is determined to be 2% for PXRD method. It is commonly known that small sized crystals may be not detected by PXRD even if their concentrations in the sample are above the limit of detection [12]. For this reason, DSC was applied as a second method to detect crystals. The DSC patterns of samples with temperature ranging from 30 to 180 °C were shown in Fig. 2. The pure NMD exhibited a sharp endothermic peak around 126 °C due to the melt of crystalline drug and no similar peak was observed in DSC pattern of HPMCAS. Physical mixture showed a relatively weak endothermic peak at 124.7 °C, while no peak was observed in the SD_8. So, it meant that the physical mixture didn't have the

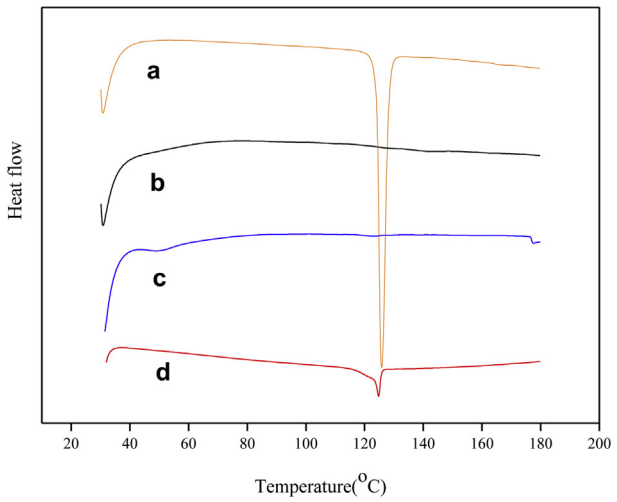

Fig. 2 – Differential scanning calorimetry (DSC) thermograms. (a) NMD; (b) HPMCAS-LF; (c) SD_8; (d) physical mixture of NMD and HPMCAS-LF.

same characteristic as the SD. The difference between them was due to the fusion and stir, it revealed that some interaction had happened between the drug and the carrier in the SD. Compared with the pure NMD and the physical mixture, the DSC result of Fig. 2c indicated that the drug in SD was possibly converted into amorphous status which could increase the dissolution rate and improve solubility, in agreement with the PXRD observations.

3.2. *Dissolution studies*

3.2.1. *Dissolution results of nimodipine solid dispersion (NMD-SD)*

NMD was a poorly water-soluble drug with an equilibrium solubility of 3.86 μg/ml in purified water. In this part, we selected 900 ml pH 1.2 and 900 ml pH 6.8 solution as dissolution media without any surface active agent as solubilizer. So this investigation was performed under non-sink condition. Under non-sink condition, SD might lead to a temporary supersaturation in the dissolution media. Therefore, non-sink condition was a better differentiation of SD formulations and comparison of the degree of supersaturation reached which depended upon dissolution of the powder and the ability of the enteric polymer to inhibit precipitation of NMD [12].

Comparing the 6 kinds of solid dispersions using different types of HPMCAS with each other, it showed that all of the solid dispersions dissolved not more than 10% in pH 1.2 dissolution media in 2 h (Fig. 3A). Moreover, the dissolution rate and the cumulative percent drug released (%) of the enteric solid dispersions were lower than the pure drug, the characteristic was dominated by the carrier which did not dissolve at pH 1.2. However, there were differences among the six kinds of solid dispersions, if we considered the less the drug released from the enteric SD in pH 1.2 dissolution media, the better the carrier was. We could conclude from Fig. 3A: the order of the type was HPMCAS-HF > HPMCAS-MG > HPMCAS-MF > HPMCAS-HG > HPMCAS-LF > HPMCAS-LG.

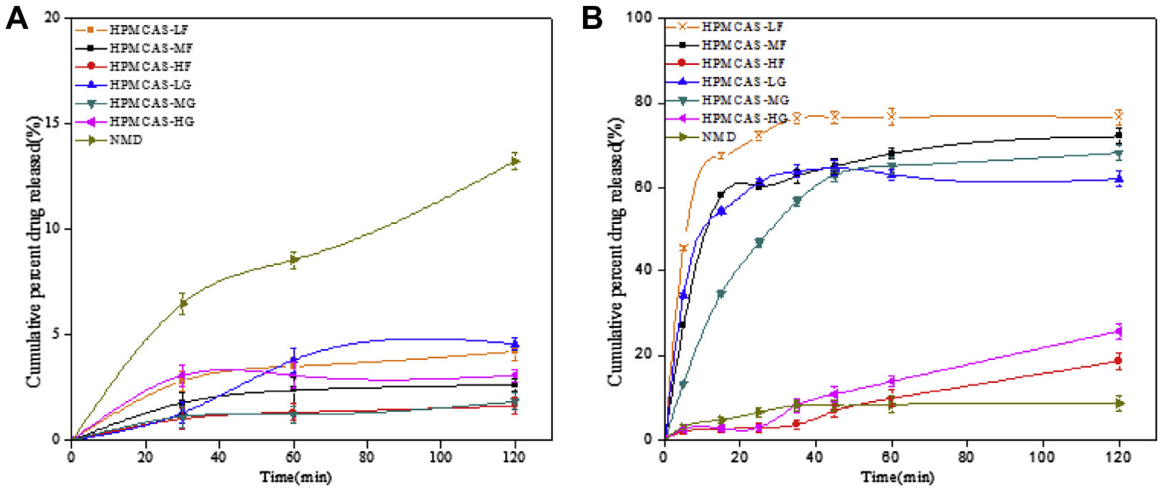

Fig. 3 – The dissolution profiles of solid dispersions using different types of HPMCAS as carrier in pH 1.2 (A) and pH 6.8 (B) dissolution media for 2 h (n = 3, mean ± SD).

Fig. 3B showed that there was markedly different dissolution behavior of enteric solid dispersions with different types of HPMCAS in pH 6.8 solution. An increase in cumulative percent drug released (%) was observed as the enteric polymer dissolved and released the amorphous NMD within the polymer leading to the maximum extent of released for all solid dispersions. The sample (SD_0) with HPMCAS-LF had the fastest dissolution rate, the most NMD (76.6%) released and superior stability during 120 min. In another word, the curve prompted that HPMCAS-LF was the most fitting carrier for NMD in this experiment. The reason may be the fusion temperature of SD_0 during preparation was 126 °C which was the closest to NMD melt point (123 °C), it might result in better interaction between NMD and the carrier.

To investigate whether the combined carriers were superior to the single carrier in improving dissolution of poorly water-soluble drug by adopting SD method, we chose HP-55 and HPMCAS as the combined carriers and HPMCAS as the single carrier. The dissolution curve was listed in Fig. 4. Single carrier had shown excellent effect in increasing dissolution rate and maximum amount of drug released while the combined carriers had not inhibited the precipitation of NMD completely during 60–120 min.

Then we selected HPMCAS-LF as carrier to prepare SD with the HPMCAS-LF/NMD ratio ranging from 1 to 5. The dissolution profiles were displayed in Fig. 5. In pH 1.2 media, the enteric solid dispersion released much less than the pure drug due to the pH dependence of carrier. With the HPMCAS-LF/NMD ratio increasing, the cumulative percent drug released (%) became lower and lower, however, the distinctions among the enteric solid dispersions were not obvious (Fig. 5A). When the pH value of dissolution media reached 6.8, the maximum amount of drug released was observed (Fig. 5B). The highest cumulative percentage of the drug dissolved from the preparations was 81.7% (SD_{11}, NMD:HPMCAS-LF = 1:5), the minimum result was 57.9% (SD_7, NMD:HPMCAS-LF = 1:1), and there was no significant difference among others (SD_8, NMD:HPMCAS-LF = 1:2; SD_9, NMD:HPMCAS-LF = 1:3; SD_{10}, NMD:HPMCAS-LF = 1:4) of which the maximum cumulative percentage was about 80%. In view of the amount of carrier used in the preparation and the maximum cumulative percentage of drug released, we chose SD_8 as the most superior SD formulation.

To judge whether the carrier or the SD technology contributed to the enhancement of solubility and dissolution rate, we compared the differences among NMD, SD_8 and physical mixture of NMD and HPMCAS-LF. It could be found that, in pH 6.8 dissolution media, the cumulative percent drug released (%) of SD_8 was 2.2 times that of physical mixture and the dissolution rate of SD_8 was much more fast than that of physical mixture, moreover, the dissolution behavior of physical mixture was a little better than that of the pure drug. The results indicated that the carrier accelerated the dissolution of NMD from physical mixture in a certain degree, and it also demonstrated that the SD technology was necessary in improving the solubility and increasing the dissolution rate (Fig. 6). The mechanism of SD was that it was a method which could affect both specific surface area and solubility. The release rate of the resultant formulation was greatly affected

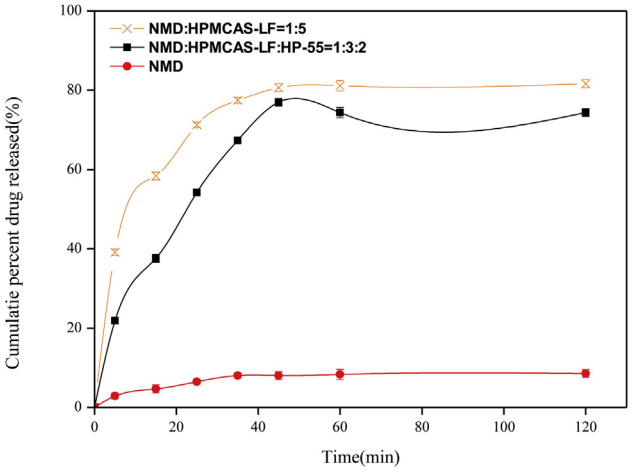

Fig. 4 – The dissolution profiles of solid dispersions using HPMCAS as single carrier and HPMCAS/HP-55 as combined carriers in pH 6.8 dissolution media for 2 h (n = 3, mean ± SD).

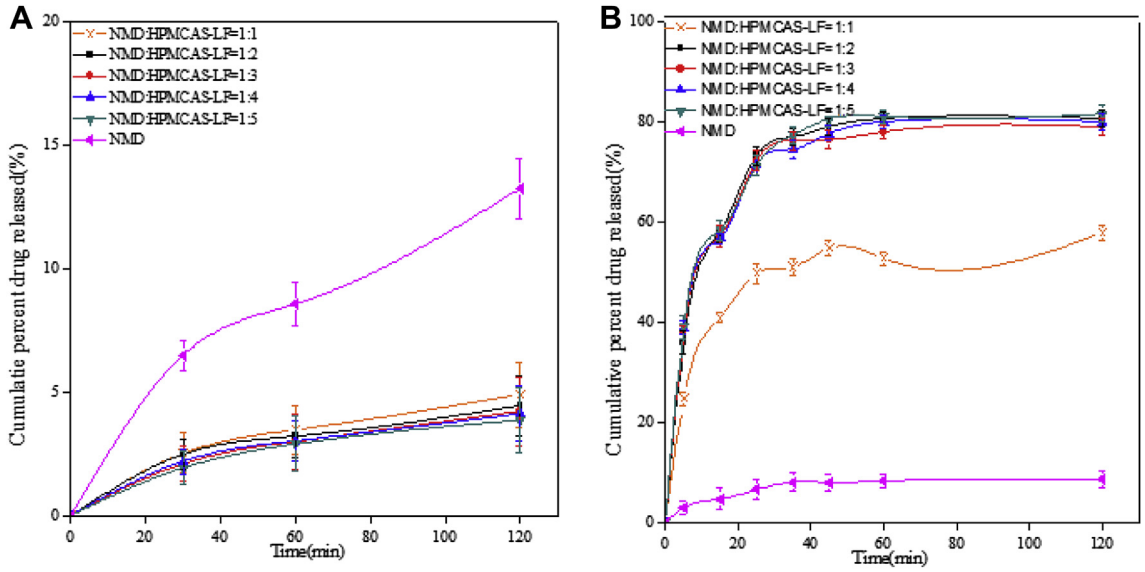

Fig. 5 – The dissolution profiles of solid dispersions with different ratio of carriers in pH 1.2 (A) and pH 6.8 (B) dissolution media for 2 h (n = 3, mean ± SD).

by the physical state of the dispersed drug, which in turn was defined by the solubility of the drug in the polymer, the method of preparation, the use of excipients, etc [10].

3.2.2. *The release profiles for tablets comprising NMD solid dispersion*

We expected that the tablets released less than 10% in the artificial gastric acid in the initial 2 h and release 20–35%, not less than 75%, more than 90% at 4 h, 10 h and 14 h respectively in the artificial intestinal fluid. The release curves of tablets containing enteric solid dispersion were tested under sink condition by adding 0.5% sodium dodecyl sulfate (SDS) into the dissolution media, the dissolution media were 750 ml pH 1.2 media (2.0 g NaCl, 7.0 ml HCL and H_2O) for the first 2 h followed by pH 6.8 phosphate buffer solution (addition of 250 ml of 0.2 M sodium triphosphate buffer) for the following 12 h, the results were given in Fig. 7. In Table 2, for formulation 1 and 5, the release rate was too fast during 2~4 h and the phenomenon indicated that the amount of MCC might be a little higher. Formulation 2 and 4 showed excessively low dissolution rate because of the use of Kollidon® SR or Eudragit® RS PO. Foumulation 3 released 2.4% in the artificial gastric acid in the initial 2 h and released 32.1%, 75%, 91% at 4 h, 10 h and 14 h respectively in the artificial intestinal fluid. According to the demand, Formulation 3 was the most superior one among the five formulations in Table 2.

There were many mathematical models for drug release/dissolution from solid pharmaceutical dosage forms. In this

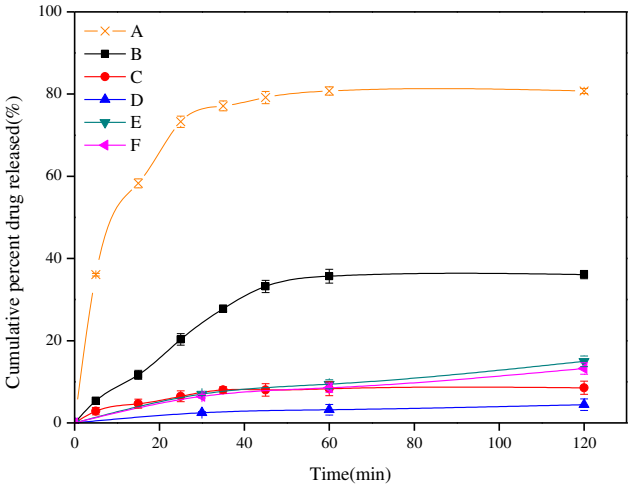

Fig. 6 – The dissolution profiles of solid dispersion, physical mixture and the pure drug. (A) SD_8 in pH 6.8 dissolution media; (B) physical mixture of SD_8 in pH 6.8 dissolution media; (C) NMD in pH 6.8 dissolution media; (D) SD_8 in pH 1.2 dissolution media; (E) physical mixture of SD_8 in pH 1.2 dissolution media; (F) NMD in pH 1.2 dissolution media (n = 3, mean ± SD).

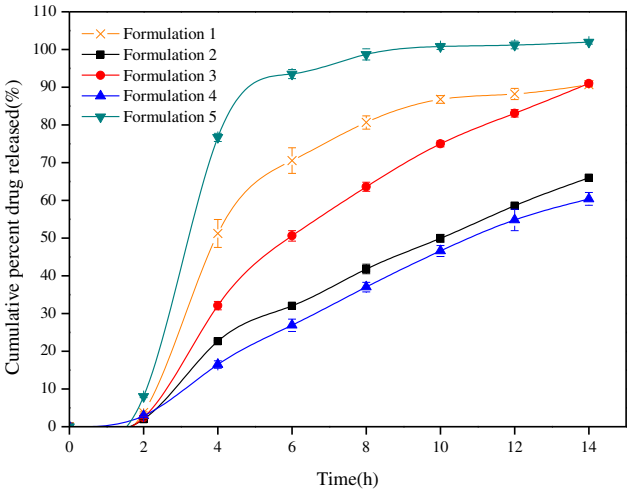

Fig. 7 – The release profiles of NMD delayed-release tablets (Table 2) in 750 ml pH 1.2 media for the first 2 h followed by pH 6.8 PBS for the following 12 h (n = 3, mean ± SD).

Table 3 – Fitted equations of NMD delayed-release tablets.

Models	Equation	Correlation coefficient
Zero order	$M_t/M_\infty = 0.07004t + 0.14807$	$r = 0.9631$
First order	$\ln(1 - M_t/M_\infty) = -0.17354t - 0.02448$	$r = 0.9984$
Higuchi	$M_t/M_\infty = 0.26187t^{0.5} - 0.00479$	$r = 0.9966$

t: time, M_t/M_∞: cumulative percent drug released (%).

work, we chose several mathematic models such as zero order, first order, Higuchi equation to imitate the drug release curves of formulation 3 in pH 6.8 dissolution media. Zero order model followed the characteristic that pharmaceutical dosage forms released the same amount of drug by unit of time and it was the ideal release method of drug release in order to achieve a pharmacological prolonged action. For first order model, the drug released from pharmaceutical dosage forms in a way that was proportional to the amount of drug remaining in its interior, it meant that the amount of drug released by unit of time diminish. In this way, a graphic of the decimal logarithm of the released amount of drug versus time would be linear [13]. Higuchi equation described drug release as a diffusion process based in the Fick's law, square root time dependent. The fitting results about delayed-release tablet were listed in Table 3. The in vitro release profiles were expressed most fitly by first-order release equation (R = 0.9984).

In order to discuss the drug release mechanism of formulation 3, we imitated the drug release profile using Peppas equation: $M_t/M_\infty = kt^n$; Where M_t/M_∞ was the cumulative percent drug released (%) in time t, k was the release rate constant, n was the characteristic parameter representing release mechanism. Peppas equation could be used for analysis of dissolution of solid dosage forms in differently geometrical shape under sink condition. For a tablet, when $n < 0.45$, the mechanism was Fickian diffusion; when $n > 0.89$, it was matrix erosion; when $0.45 < n < 0.89$, it was the combination of matrix erosion and diffusion. The fitting result was :$M_t/M_\infty = 0.23081t^{0.55746}$ ($r = 0.9986$); because of $0.45 < n < 0.89$ ($n = 0.55746$), the release mechanism of formulation 3 was not only diffusion but also matrix erosion. Moreover, the dominant release mechanism was diffusion. In the initial stage of the dissolution test, the swelling material (such as PEO) in tablets started to uptake water in the pH 1.2 buffer medium, resulting in an expansion of the tablets volume. This variation would decrease the density of the tablets, and a less viscous gel was generated. As a consequence, there was a faster release profile at the following 2 h in pH 6.8 buffer medium mainly due to the release mechanism of erosion, and then the drug-delivering behavior was slowing down when diffusion mechanism held the dominant position at the sequent time.

4. Conclusion

The present study demonstrated the development of an NMD delayed-release tablet formulation using SD. The dissolution rate and solubility of NMD solid dispersions were improved compared with the pure drug. DSC and PXRD were adopted in this investigation to identify the physical state of the drug in SD and it proved that the crystalline NMD transformed into the amorphous state after preparation. To evaluate the delayed-release tablets, we conducted the in vitro release study, the delayed-release tablets released less than 10% in the artificial gastric acid in the initial 2 h and release 32.1%, not less than 75%, more than 90% at 4 h, 10 h and 14 h respectively in the artificial intestinal fluid. Moreover, the in vitro release profiles were expressed most fitly by first-order release equation (R = 0.9984), the release mechanism of tablets was not only diffusion but also matrix erosion, and the dominant release mechanism was diffusion.

Acknowledgment

This project is supported by special construction projects fund which belongs to "Taishan Scholar—Pharmacy Specially Recruited Experts".

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