Investigation of polyethylene oxide-based prolonged release solid dispersion containing isradipine

Thao Truong-Dinh Tran*, Phuong Ha-Lien Tran*

International University, Vietnam National University, Ho Chi Minh City, Vietnam
*Correspondence: ttdthao@hcmiu.edu.vn - thlphuong@hcmiu.edu.vn

The aim of the study was to press a synergistic act of a formulation: (1) enhancing the dissolution rate of a poorly water-soluble drug; (2) controlling the release rate of the drug. There is still little published research on such a formulation. The model drug used in the current study is isradipine (IS), a calcium channel blocker of the dihydropyridine class. To fulfill the expected target, solid dispersion containing IS was first prepared with the carrier polyethylene glycol 6000 (PEG 6000) with the melting method and then polyethylene oxide N-60K (PEO N-60K) was utilized to induce drug release in a controlled manner. Physicochemical properties of the solid dispersion and physical mixture were characterized by powder x-ray diffraction (PXRD) and Fourier transform infrared (FTIR) spectroscopy to investigate the structural behavior of drug and IS-PEG interactions, respectively. Preparation of such a formulation not only enhanced but also controlled the drug dissolution rate in both simulated gastric (pH 1.2) and intestinal (pH 6.8) media. This result should be a consideration for pharmaceutical scientists in maintaining the desired blood levels of drugs with narrow therapeutic fluctuation ranges for extended periods of time after a single administration.

Key words: Prolonged release – Solid dispersion – Poorly water-soluble drug – Enhanced drug release rate – Prolonged release manner – Physicochemical characterization.

Improving the solubilization of poorly water-soluble drugs is very important because it determines the therapeutic efficacy of a drug product. Despite high permeability, many promising new chemical entities (NCEs) are generally only absorbed in the upper small intestine, so absorption is reduced significantly after the ileum i.e., there is a small absorption window. Therefore, to overcome dissolution rate limiting absorption and low bioavailability of these drugs, various solubilization strategies have been developed. Nevertheless, solid dispersion (SD) has been widely used and is considered a common method enhancing the solubility, dissolution rate, and bioavailability of poorly soluble drugs [1-5]. Hydrophilic polymers, such as polyethylene glycol, hydroxypropylcellulose, polyvinylpyrrolidone, etc., are commonly used in SD preparation. However, the SD generally tends to be immediate-release forms with the inherent drawbacks of high peak drug concentrations in the blood, short times following administration when drug concentrations in the blood reach their tmax and relatively short durations of effective concentration levels in the blood [6]. To overcome such problems, an interest in a strategy for the combined systems of improved solubilization and prolonged release of poorly water-soluble drugs has been raised recently [7, 8]. These dosage forms provide an immediately available dose for an immediate action followed by a gradual and continuous release of subsequent doses to maintain the plasma concentration of poorly water-soluble drugs over an extended period of time. Moreover, prolonged release dosage forms containing SDs have been considered effective systems for treatment over a long period and could be prepared using polymer-based systems [9]. However, there have been few such studies reported so far. A prolonged release-solid dispersion (PR-SD) comprising both functions of SD and prolonged release for poorly water-soluble drugs has therefore been investigated in the current study. Isradipine (IS), a calcium antagonist for treating hypertension [10] and known to be poorly water-soluble in aqueous solution (less than 10 μg/mL) [11], was chosen as a model drug. Moreover, IS has unfavorable properties that make it a candidate for a research aiming to enhance its bioavailability. It is 90-95 % absorbed and is subject to extensive first-pass metabolism, resulting in a relatively low bioavailability of about 15-24 % [12, 13]. Due to the short half-life of 8 h [14, 15], IS is also a good candidate for prolonged release dosage form in 24 h. So far, isradipine has been reportedly used as the model drug in previous research into buccal tablets [12], osmotic system [16-18] and transdermal delivery system [19]. Still, the drug has never been introduced into the formulation of prolonged release solid dispersion. The polymer family of ethylene oxide i.e., polyethylene glycol 6000 (PEG 6000) and polyethylene oxide N-60K (PEO N-60K) were chosen as a hydrophilic carrier for SD preparation and polymer for prolonged release dosage form, respectively, due to some advantages such as flexibility, low toxicity, unlikelihood of specific interactions with biological chemicals, etc. The SDs of drugs with PEG 6000 may be useful to solve various problems such as enhancement of stability, solubility and dissolution rate [20, 21]. Although PEG 6000 can be used in both solvent and melting method for SD preparation, the melting method was chosen in this study due to the preferable environmental and cost aspects. Drug dissolution studies were performed in both simulated gastric (pH 1.2) and intestinal (pH 6.8) media to figure out if the drug release behaviors satisfied the enhanced release rate in controlled manner as compared to the pure drug. The possible interaction between the drug and PEG was investigated through Fourier transform infrared spectroscopy (FTIR). Moreover, the change of drug structure, especially for the drug crystallinity, if any, was also studied through powder x-ray diffraction (PXRD) analysis.

I. MATERIALS AND METHODS

1. Materials

Lactose was obtained from Meggle (Wasserburg, Germany). Magnesium stearate was purchased from Katayama Chemical Co. (Osaka, Japan). Polyethylene glycol 6000 (PEG 6000) was purchased from Yakuri Pure Chemicals Co., Ltd. (Osaka, Japan). Polyethylene oxide N-60K (PEO N-60K) was provided by the Dow Chemical Company (United States). The solvents used were high performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade and were used without further purification.

2 Methods

2.1. HPLC analysis

IS concentration was determined by HPLC system with a Luna 5 μ C18 analytical column (150 × 4.6 mm). The mixture of methanol, deionized water and acetonitrile (7:3:5) was used as a mobile phase. The UV detector was set at 325 nm to analyze the column effluent. The entire solution was filtered through a 0.45 μM membrane filter (MilliporeCorp., Bedford) and was degassed prior to use. Twenty-microliter samples were injected into HPLC system for analysis.

2.2. Preparation of SD containing isradipine

The SD was prepared by the melting method. First, PEG 6000 was melted at 160 °C by stirring hot plate. IS was then incorporated in melted PEG 6000. The resulting binary mixtures were constantly stirred for 15 min to dissolve and mix IS with PEG 6000. When a clear solution was obtained, the mixture was immediately frozen at -20 °C in a deep freezer for 30 min. The SD sample was cooled down to room temperature in 30 min. The drug crystallinity of this sample was then investigated via DSC and PXRD. In order to prepare tablets, the SD sample was ground and passed through a 60-mesh sieve. The SDs consisting of IS and PEG 6000 were prepared in weight ratios 1:3, 1:6 and 1:9. The detailed formulations are described in *Table I*. To ensure the absence of degradation, IS concentration of the SD sample was determined by HPLC before tableting.

2.3. Preparation of prolonged release solid dispersion tablet

The SD sample was blended with PEO N-60K, lactose and finally with magnesium stearate. The blend homogeneity was confirmed by quantification of the IS amount in the mixture. This sample was directly compressed into a 200 mg tablet equivalent to 5 mg IS by round punches and dies with a 6-mm diameter. The hardness was controlled at 25 ± 2 N and a dwell time of 10 s. The detailed formulations were also described in *Table I*.

2.4. Dissolution studies

The pure IS, SD powders and tablets equivalent to 5 mg IS were exposed to 900 mL dissolution media. Dissolution of SD powder was performed in enzyme-free simulated gastric fluid (pH 1.2) and enzyme-free simulated intestinal fluid (pH 6.8) for 120 min using a USP apparatus II (50 rpm, 37 °C). Dissolution of tablet was performed according to previous research [22]. Firstly, a dissolution test was performed in enzyme-free simulated gastric fluid (pH 1.2) for 2 h using a USP apparatus I (100 rpm, 37 °C). At the end of 2 h, the gastric fluid was discarded and replaced with enzyme-free simulated intestinal fluid (pH 6.8). Dissolution testing was continued until 24 h. Samples were withdrawn at predetermined intervals and replaced with an equivalent amount of fresh medium to maintain a constant dissolution volume. The concentrations of IS were finally analyzed by HPLC as described above.

2.5. Powder x-ray diffraction (PXRD)

A D5005 diffractometer (Bruker, Germany) using Cu-Kα radiation at a voltage of 40 kV, 50 mA, was used to investigate PXRD patterns of pure IS, PEG 6000 and all SD samples. To understand the clear functioning mechanism of dissolution enhancement, the plain binary SD of pure IS was separately mixed with PEG 6000 to obtain physical mixtures (PM). The samples were scanned in increments of 0.02° from 5 to 60° (diffraction angle 2θ) at 1 s/step, using a zero background sample holder.

2.6. Fourier transform infrared spectroscopy (FTIR)

A FTIR spectrophotometer (Model Excaliber Series UMA-500, Bio-Rad, United States) was used to investigate the spectra of pure IS, PEG 6000, PM, SD samples. The wavelength was scanned from 500 to 4000 cm^{-1} with a resolution of 2 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr.

2.7 Contact angle measurement

Pure IS and SD samples were dissolved in ethanol of a 5 % concentration. The solution was then spin-coated on to a silicon (100) wafer at a speed of 3000 rpm for 30 s using a Head-Way PM101DT-R485 spinner (Shinu MST Co. Ltd.) and then dried in air to form a thin film. Contact angles were measured by the sessile drop technique on a contact angle gonimeter (DSA 100, Kruss GmbH, Germany). In each experiment, a drop of deionized water was placed on the surface of the thin film at room temperature. The measurements were taken five times by reading directly.

2.8 Solubility study

An excess of IS (1 mg) was added to the tube containing either 1 mL of water, 1 mL of enzyme-free simulated gastric fluid (pH 1.2), 1 mL of enzyme-free simulated intestinal fluid (pH 6.8) or solution containing 5 % excipient in water and shaken in a water bath at 37 °C (100 rpm) for 72 h. The aliquot was filtered through a 0.45 μm membrane filter (Millipore, United States) and immediately diluted with the mobile phase for determination of IS content by HPLC analysis.

II. RESULTS AND DISCUSSION

1. Solubility and dissolution study

Our preliminary study showed that IS has low solubility in water and intestinal fluid (6.98 ± 0.01 and 8.64 ± 0.05 μg/mL, respectively), but has a higher solubility in gastric fluid (114.01 ± 1.17 μg/mL). Interestingly, incorporating 5 % PEG 6000 in water (w/v) increased drug solubility (128.63 ± 2.72 μg/mL). These results suggested that molecular interaction between IS and PEG 6000 possibly occurred to increasing the drug solubility.

The formulation of poorly water-soluble drugs for oral delivery is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. The most attractive option for increasing the release rate is through solid dispersion formulation approaches. Therefore, the solid dispersion formulations of IS with carrier PEG 6000 at various ratios were screened for the selection of the most suitable incorporation. Pure IS was compared with other SD formulations for dissolution rate at pH 1.2 and pH 6.8 (*Figures 1 and 2*, respectively). The incorporation of PEG 6000 as the carrier in the solid dispersion at three ratios in the study (F1, F2, F3) all showed the increase in the dissolution kinetics of IS from polyethylene glycol SDs in both media while drug release from the pure material was almost zero, indicating the poorly water-soluble property of the drug. Among the SDs formulated with PEG 6000, the incorporation of PEG 6000 and

Table I - Formulation compositions of SD powder (F1, F2, F3) and prolonged release solid dispersion tablet (F4, F5).

Formulation	IS (mg)	PEG 6000 (mg)	PEO N-60K (mg)	Lactose (mg)	Magnesium stearate (mg)	Total (mg)	Comments
F1	5	15				20	SD powder
F2	5	30				35	SD powder
F3	5	45				50	SD powder
F4	5	45	40	108	2	200	Tablet
F5	5	45	60	88	2	200	Tablet