International Journal of Pharmaceutics 484 (2015) 228–234

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

Development of a modified – solid dispersion in an uncommon approach of melting method facilitating properties of a swellable polymer to enhance drug dissolution

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ARTICLE INFO

Article history:
Received 6 November 2014
Received in revised form 20 February 2015
Accepted 27 February 2015
Available online 28 February 2015

Keywords:
Solid dispersion
Melting method
Swellable polymer
Poorly water-soluble drug
Controlled release

ABSTRACT

The study aimed to develop a modified-solid dispersion method using a swellable hydrophilic polymers accompanied by a conventional carrier to enhance the dissolution of a drug that possesses poor water solubility. Two swellable polymers (hydroxypropyl methylcellulose and polyethylene oxide) were swelled in melted polyethylene glycol 6000 (PEG 6000) in different ratios and under different conditions. The type, amount, and, especially, incorporation method of the swellable polymers were crucial factors affecting the dissolution rate, crystallinity, and molecular interaction of the drug. Interestingly, the method in which the swellable polymer was thoroughly mixed with the melted PEG 6000 as the first step was more effective in increasing drug dissolution than the method in which the drug was introduced to the melted PEG 6000 followed by the addition of the swellable polymer. This system has potential for controlling drug release due to high swelling capabilities of these polymers. Therefore, the current study can be considered to be a promising model for formulations of controlled release systems containing solid dispersions.

1. Introduction

Solid dispersion (SD) is a potential approach in enhancing dissolution and bioavailability of poorly water-soluble drugs. Advantages of the technique such as simplicity, economization, and others have been widely reported (Vasconcelos et al., 2007). There are two basic different preparation methods of SD including melting method and solvent evaporation method (Tran et al., 2009, 2010). Melting method was first demonstrated by Sekiguchi and Obi (1961). The product was prepared by melting drug with carrier, then cooling and pulverization. In the melting process, high mobility of carrier would change the combination of drug (van Drooge et al., 2006). In solvent evaporation method, drug and carrier were completely dissolved in a volatile solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane (Hasegawa et al., 2005; Lloyd et al., 1999; Rodier et al., 2005) at a low temperature to avoid thermal degradation of drug and carrier (Won et al., 2005). The later method has some disadvantages such as high preparation cost, incomplete solvent removal, alteration in product performance with the change of condition applied (Vasconcelos et al., 2007).

The swellable hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) were introduced in this study to modulate drug release from a SD (Tran et al., 2011; Tran and Tran, 2013). As they are hydrophilic, these polymers may improve the solubility of poorly water-soluble drugs, and their swellable properties may be exploited to promote controlled drug release. The utilization of these two polymer properties in one system might facilitate the development of specialized drug delivery systems by both enhancing drug solubility and controlling the release of poorly water-soluble drugs. This hypothesis was tested herein through the preparation of SDs. However, these polymers are difficult to melt at high temperatures for SD preparation. On the other hand, disadvantages are usually met in the solvent method as mentioned above. Moreover, drugs may be precipitated during solvent removal, leading to the failure of the method intended to enhance drug solubility. Slow drug dissolution rates result when the drugs are not well distributed in the polymer. Therefore, the SD method is not always a successful approach to

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http://dx.doi.org/10.1016/j.ijpharm.2015.02.064
0378-5173/

improve drug solubility. Thus, in this paper, an SD system using the melting method was developed as a new feasible technique using swellable hydrophilic polymers. The system was fabricated not only to increase the dissolution rates of poorly water-soluble drugs, but also to potentially control the release of those drugs. Curcumin (CUR), a poorly water-soluble drug with many potential applications, was used as the model drug in this study. The crystalline behaviors and molecular interactions in the system were investigated to elucidate the potential of this system.

2. Materials and methods

2.1. Materials

Curcumin and sodium hydroxide (NaOH) were purchased from Guanghua Sci-Tech Company (China). Hydroxypropyl methyl cellulose (HPMC 4000, HPMC 6) and polyethylene oxide N-60K (PEO) was provided by from Dow Chemical Company (USA). Polyethylene glycol (PEG 6000) was purchased from Sino-Japan Chemical (Taiwan). Methanol (MeOH) was purchased from Fisher Scientific International, Inc. (US). Hydrochloric acid (HCl) and sodium chloride (NaCl) were purchased from Xilong Chemical Industry Incorporated Company (China). Monopotassium phosphate (KH_2PO_4) was purchased from Wako Pure Chemical Industries (Japan).

2.2. Methods

2.2.1. Preparation of SDs

Melting method was used for preparation of SDs. Following are some factors that were varied to prepare different SDs for evaluation of drug release rate: swellable polymers (HPMC 6, HPMC 4000, and PEO), the polymer ratio, and combination method between drug and polymers (Table 1). The SDs were finally stored in a dry place and protected from light until further use.

Two combination methods were differentiated by the order of incorporation of drug and swellable polymer into melted PEG 6000. In method I, PEG 6000 and drug had been thoroughly mixed before the polymer was added in the mixture. PEG 6000 was melted at 190 °C, and CUR was then added under stirring until a uniform mixture was obtained. Then the swellable polymer was dispersed in the mixture to obtain SDs in semisolid form which were finally cooled at room temperature (25 °C) before use. In method II, PEG 6000 and swellable polymer were mixed before the drug was added into the melted mixture. Every other step was conducted as it was in method I. The melting temperature was controlled and the mixture was stirred on digital stirring hot plates (Thermo Scientific, Germany) during the preparation process.

2.2.2. Dissolution studies

Drug dissolution was studied with SDs at 37 ± 0.5 °C (50 rpm, paddle apparatus, DT70 Pharmatest, Germany) according to the USP 30 pharmacopoeia. Buffer (pH 1.2 or pH 6.8, 900 ml in each dissolution vessel) was used as the dissolution medium. Sample aliquots (1 ml) were collected from the media at predetermined intervals of 10, 20, 30, 60, 90, and 120 min. 1 ml of withdrawn sample was compensated by adding 1 ml of the corresponding fresh buffer.

2.2.3. HPLC analysis

The quantification of CUR was performed using an Ultimate 3000 HPLC system (Thermoscientific Inc., USA). The mobile phase was 4:1 methanol/acetic acid 2%. The flow rate was maintained at 1.2 ml/min. The UV/vis detector was set to a wavelength of 425 nm. 20 μl of sample was injected to HPLC system.

2.2.4. Characterization by X-ray diffraction (PXRD)

In this study, pure CUR, PEG 6000, HPMC 4000, physical mixture (PM), and SDs were analyzed by PXRD. Diffraction patterns were recorded by a Powder X-ray diffractometer (Bruker' D8 Advance Series PXRD, Germany) using Ni-filtered, CuKα (λ = 1.54060 Å) radiation at a voltage of 40 kV and at a current of 40 mA. Samples were held on quartz frame. The sample was scanned in a 2θ from 5° to 50° with a receiving slit 0.1 mm (a step size of 0.021° at 2θ/s).

2.2.5. Characterization by Fourier transform infrared spectroscopy (FTIR)

The physicochemical properties of CUR, PEG 6000, HPMC 4000, PM, and SDs were characterized by using a Bruker Vertex 79 FTIR spectrometer (Germany). KBr pellets were prepared by mixing 1 mg of samples with 200 mg KBr. The wavelength was 500–4000 cm^{-1} and the resolution was 2 cm^{-1}.

2.2.6. Solubility test

Excess CUR was added to the tubes containing 1 ml of various media (pH 1.2 and pH 6.8). The resulting mixtures were shaken at 100 rpm at 37 °C for 48 h in a water bath. The tubes were then centrifuged at 13,000 rpm for 15 min. The supernatant was diluted for the determination of drug concentration by HPLC.

2.2.7. Statistical analysis

All data were presented as mean ± standard deviation. The statistical significance of the differences was determined using an analysis of variance (ANOVA) ($P < 0.05$ or 0.01).

3. Results and discussion

3.1. Dissolution and solubility studies

Our preliminary study showed that CUR was poorly soluble and had lower solubility in acidic medium than basic medium. Specifically, solubility of CUR at pH 1.2 and pH 6.8 were 7.230 ± 0.35 and 12.6 23 ± 3.54, respectively. For this reason, most

Table 1
Formulation compositions of SDs.

Formulation	Cur. (mg)	PEG 6000 (mg)	HPMC 4000 (mg)	HPMC 6 (mg)	PEO (mg)	Ratio	Mass (mg)	Stirring time	Combining method
F1	30	120	–	–	–	1:4	150	5 min	I
F2	30	240	–	–	–	1:8	270	5 min	I
F3	30	120	–	60	–	1:4:2	210	5 min	I
F4	30	120	60	–	–	1:4:2	210	5 min	I
F5	30	120	–	–	60	1:4:2	210	5 min	I
F6	30	120	120	–	–	1:4:4	270	5 min	I
F7	30	240	120	–	–	1:8:4	390	5 min	I
F8	30	240	180	–	–	1:8:6	450	5 min	I
F9	30	240	120	–	–	1:8:4	390	5 min	II
F10	30	240	180	–	–	1:8:6	450	5 min	II