European Journal of Pharmaceutical Sciences 114 (2018) 346–355

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Alginate as a potential diphase solid dispersion carrier with enhanced drug dissolution and improved storage stability

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ARTICLE INFO

Keywords:
Solid dispersion
Alginate
Miscibility
Hansen solubility parameter
Raman mapping
Stability

ABSTRACT

The objective of this study was to explore the feasibility of using alginate as a promising diphase solid dispersion carrier to enhance dissolution rate of BCS II drugs with improved stability. Taking lovastatin and indomethacin as model drugs, solvent evaporation method was used to prepare solid dispersions. The drug/polymer compatibility was predicted by Hansen solubility parameter and the drug/polymer ratio was screened based on dissolution study, drug existing state in solid dispersion was characterized by DSC and XRPD. Accelerated stability of the solid dispersion was assessed and compared with that of HPMCAS based system. Phase behavior of the solid dispersion before and after stability study was characterized using polar microscope and Raman mapping. It was found that the optimal drug/alginate ratio was drug dependent and drug existing state was related to drug/alginate miscibility. Stability studies revealed that alginate improved the stability of solid dispersions regardless of drug existing state and a better stability was obtained compared to HPMCAS based system. Raman mapping and SEM study revealed that micro phase separation of solid dispersion was the main reason for the slight decrease in drug dissolution after accelerating experiment. In conclusion, alginate can be used as a promising diphase solid dispersion carrier with significantly improved dissolution rate and storage stability.

1. Introduction

Nowadays a large number of newly explored drug candidates are highly hydrophobic (Lombardino and Lowe 2004; Obeidat and Sallam 2014). Due to the low aqueous solubility, these drugs frequently present low dissolution rate in the gastrointestinal tract and therefore poor bioavailability (Keck and Muller 2006). Thus, new strategies are in need to solve these problems, especially for biopharmaceutical classification system II (BCS II) drugs, and their dissolution rate in the gastrointestinal fluids has been identified as the main absorption rate-limiting step (Fahr and Liu 2007; Knopp et al. 2016).

So far, different formulation strategies have been employed to enhance the dissolution rate of BCS II drugs and consequently improve their oral bioavailability, such as co-crystal (de Mohac et al. 2016), solid dispersion, salts formation, co-solvents, and micronization (Khadka et al. 2014). Among them, solid dispersion approach is the most commonly used one with simple preparation procedures (Raimi-Abraham et al. 2015). The solid dispersion consists of two or more different ingredients, generally a hydrophilic excipient as the carrier and a hydrophobic model drug. The dispersed drug could exist in its amorphous or crystalline state in the carrier. It is well known that when a crystalline state drug is converted into amorphous state, the dissolution rate and water solubility could be remarkably increased since higher intermolecular energy and molecular mobility are obtained compared to the crystalline counterpart. Therefore, in general, amorphous solid dispersion is highly desirable in order to enhance drug dissolution rate. However, the main concern of amorphous solid dispersion is the poor stability. It is because the drug substance existed in its amorphous state has high tendency to recrystallize within pharmaceutically relevant timescales, leading to particle size increase and therefore reduced dissolution rate. Thus, it is highly desired to search for novel solid dispersion carriers, which could not only enhance drug dissolution rate but also maintain the stability in a long term.

Sodium alginate is a hydrophilic polysaccharide extracted from the brown seaweeds' cell walls. It is composed of 1–4 linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) monomers, in alternative blocks of MM, MG and GG arranged in an anomalous pattern (George and Abraham 2006). Alginate has been widely applied in various areas including bioengineering, food industry as well as pharmaceutical field (Ruvinov and Cohen 2016). It can be used as hydrogel former and has been well explored for the development of micro- or nanoparticles (Devi and Kakati 2013). It was also reported that in case there is

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https://doi.org/10.1016/j.ejps.2017.12.028
Received 30 September 2017; Received in revised form 7 December 2017; Accepted 29 December 2017
Available online 03 January 2018
0928-0987/

molecular interaction between alginate and drug, alginate could be used as an amorphous solid dispersion carrier with enhanced drug dissolution rate (Borba et al., 2016). While, for most of BCS II drugs, alginate based amorphous solid dispersions are difficult to form due to limited molecular interaction between alginate and the drugs. Thus, it is essential to investigate whether alginate could also improve the dissolution rate of BCS II drugs independent of drug existing state and drug alginate miscibility. Our previous study did revealed that alginate could be used as stabilizer of nanosuspension to facilitate the dissolution rate of hydrophobic drugs without altering drug's crystalline state (Guan et al. 2017). Thus, we hypothesized that alginate might be a promising solid dispersion carrier to facilitate dissolution rate of poorly water soluble drugs without influencing drugs' existing state and with improved long term stability.

Therefore, in this study, taking lovastatin and indomethacin, two BCS II drugs with different compatibility with alginate, as drug model, the solid dispersions were prepared by solvent evaporation method, the dissolution rate improvement and the miscibility of drug/carrier on drug existing state were evaluated. The drug/polymer ratio was screened based on dissolution study and drug existing state was characterized by DSC and X-ray. The stability under accelerated condition was assessed and compared to that of HPMCAS based solid dispersion. Phase behavior of the solid dispersion after stability study was characterized using polar microscope and Raman mapping in combination with SEM.

2. Materials and methods

2.1. Materials

Lovastatin and indomethacin were purchased from Hubei Xinyinhe Pharmaceutical Co., Ltd. (Wuhan, China) and Dalian Meilun Biological Technology Co., Ltd. (Dalian, China), respectively. Alginate Protanal® LFR5/60 (SA, 60–70% G content) was provided by FMC Health and Nutrition (Philadelphia, US). Microcrystalline cellulose (MCC-PH200) and Ai-Di-Sol were gifts from FMC Health and Nutrition (Philadelphia, US). Polyplasdone XL-10 (PVPP) was provided by Asland. (USA). Hypromellose Acetate Succinate (HPMCAS-MF) was provided by Shin-Etsu Chemical Co., Ltd. (Shanghai China). Lauryl sodium sulfate (SDS) was purchased from Biotech Co., Ltd. All other chemicals were of analytical grade.

2.2. Preparation of solid dispersion

Drug loaded solid dispersion was prepared by solvent evaporation method. Briefly, the required amount of drug was weighed and dissolved in 40 mL alcohol at 60 °C in a 250 mL round-bottom flask followed by adding specific amount of alginate or HPMCAS to form dispersions. The dispersion was then evaporated using a RE-52AA rotary evaporator (YARONG Co. Ltd., Shanghai, China) under 60 °C, the samples were then dried over a period of 12 h at 40 °C to further remove the solvents under vacuum. The resultant solid dispersions were collected and pulverized using a mortar and pestle, and stored in a desiccator at room temperature until analysis.

2.3. Preparation of physical mixture

Drug/polymer physical mixture was prepared by geometric dilution method with mortar and pestle. In brief, an equal amount of lovastatin or indomethacin and polymers were firstly mixed and further diluted with polymers to the optimized drug/carrier ratio. The powder was stored in a desiccator at room temperature until further investigation.

2.4. In vitro dissolution

In vitro dissolution study was carried out using the paddle method equipped with a USP II apparatus at 37.5 ± 0.5 °C and at paddle speed of 50 rpm. Briefly, for lovastatin solid dispersion, appropriate amount of samples (containing 60 mg lovastatin) was added into 900 mL dissolution medium (0.05 M pH 6.8 phosphate buffer with 0.1% SDS). Samples (6 mL) were collected at predetermined time intervals and immediately filtered through a 0.15 μm syringe filter. After discarding the first 2 mL of filtrate, the remaining filtrate was collected and analyzed at 237 nm using a UV spectrophotometer (UNICO 2000, shanghai, China). Meanwhile, an equal volume of fresh dissolution medium was added.

For indomethacin solid dispersions, the *in vitro* release was investigated in a similar way. Appropriate amount of samples (containing indomethacin 25 mg) was added into 900 mL dissolution medium (0.05 M pH 6.8 phosphate buffer). The absorbance of indomethacin was determined at 320 nm. All experiments were carried out in triplicate.

The difference in dissolution profiles was compared using similarity factor (f_2) (Li et al. 2013), which was calculated using the Eq. (1):

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (1)$$

where n is the number of time points, T_t is the dissolution value of the test at time t and R_t is the dissolution value of the reference at time t. The release profiles were regarded as significantly different if $f_2 < 50$. No more than one experimental point should be taken into consideration after 85% of drug dissolution.

2.5. DSC

Thermodynamic analysis of the coarse drug, solid dispersions, physical mixture, and polymers were performed with differential scanning calorimetry (Mettler-Toledo). Powdered samples (3–5 mg) were weighed and the sealed aluminum pans were selected for the analysis. Indium was chosen for temperature and enthalpy calibration. The samples were scanned at a heating rate of 10 °C/min from 20 °C to 250 °C in nitrogen atmosphere. The melting temperature and drug existing state were determined from the endothermic peak of the DSC curve recorded.

2.6. XRPD

XRPD patterns were collected using an X-ray diffractometer (Xpert PRO, Panalytical, Germany) with Cu-Ka radiation generated at 45 kV and 40 mA. Solid dispersion, coarse drug, physical mixture, and carrier were analyzed in the 2θ range from 5 to 45° with a step width of 0.03° and a count time of 2 s.

2.7. SEM

The morphologies of the solid dispersion, coarse drug, polymers and physical mixture were observed by a SU8010 field-emission scanning electron microscope (Hitachi, Japan) at a 10 kV of accelerating voltage. Prior to imaging, a small amount of powder samples were sprinkled onto double-sided adhesive tape attached to an aluminum stub and the mounted samples were coated with gold under vacuum. Photographs were taken at varied magnifications to reveal surface characteristics of the powder.

2.8. Hansen solubility calculation

The Hansen solubility parameter (δ) of drug-polymeric carrier was calculated based on the group contribution method (Shi et al. 2016; Wlodarski et al. 2015). The total solubility parameter was determined from the interactions between polar interactions (δ_p), dispersion forces (δ_d) and hydrogen bonding (δ_H) of the functional groups in the molecule according to Eqs. (2)–(5). The solubility parameter unit was $MPa^{1/2}$.