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Interfacial interaction track of amorphous solid dispersions established by water-soluble polymer and indometacin

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ABSTRACT

The present work studied interfacial interactions of amorphous solid dispersions matrix of indometacin (IMC) that established using PVP K30 (PVP) and PEG 6000 (PEG) by focusing on their interaction forces and wetting process. Infrared spectroscopy (IR), raman spectroscopy, X-ray photoelectron spectra and contact angle instrument were used throughout the study. Hydrogen bond energy formed between PEG and IMC were stronger than that of PVP and IMC evidenced by molecular modeling measurement. The blue shift of raman spectroscopy confirmed that hydrogen bonding forces were formed between IMC and two polymers. The contact angle study can be used as an easy method to determine the dissolution mechanism of amorphous solid dispersions through fitting the profile of contact angle of water on a series of tablets. It is believed that the track of interfacial interactions will certainly become powerful tools to for designing and evaluating amorphous solid dispersions.

1. Introduction

It is widely known that active pharmaceutical ingredients (APIs) under development are used as solid dosage forms to exert effective and reproducible in vivo plasma concentration after oral administration. In fact, over 40% of APIs are poorly water-soluble drugs with poor absorption, and even most promising ones with high permeability are only absorbed in the upper small intestine, resulting in the reduction of absorption after the ileum (He and Ho, 2015; Vo et al., 2013). Amorphous solid dispersions that defined as molecular mixtures of poorly water-soluble drugs in hydrophilic matrix, are considered to be one of the most effective strategies to enhance the release of poorly water-soluble drugs (Keratichewanun et al., 2015; Mishra et al., 2015). Amorphous solid dispersions provide an effective method to improve the oral bioavailability of poorly water-soluble drugs by dispersing hydrophobic drug homogenously within the carrier matrix. The matrix generally consists of water-soluble polymers, such as hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP). Drug can be distributed in molecular state, fully amorphous state or nano size crystals in the solid matrix. Therefore the wetting of incorporated drugs in the matrix is increased and drug dissolution can be improved (Keratichewanun et al., 2015; Shergill et al., 2016; Shi et al., 2015; Vasconcelos et al., 2007).

Indomethacin (IMC) that belongs to one kind of non-steroidal anti-inflammatory drugs, is applied to reduce pain and swelling for the treatment of gout, osteoarthritis and rheumatoid arthritis (Li et al., 2016; Li et al., 2015a). However, the crystalline forms of IMC are poorly soluble in aqueous, thus resulting in low bioavailability and absorption in the biological system. The dissolution properties of IMC can be improved when it lacks long range order because IMC with no crystal lattice has high energy in the matrix of amorphous solid dispersions. Despite there is intensive research on amorphous solid dispersions of IMC (Ewing et al., 2014; Tajiri et al., 2015), the interfacial drug–polymer interactions have rarely been systemically studied. It has been reported that drug–polymer interactions can impact the distribution of surface active groups at the outermost atom layer in the tablet and further affect wetting. Nevertheless, these interactions can also change the mobility of polymer chain and chain–chain cohesion, which influence solvent penetration, local dissolution rate and transport of locally released drug(Sun and Lee, 2015). Particularly, drug–polymer interactions via hydrogen bond are important for increasing the stability of the amorphous state of drug. Therefore, it is certain that the study of interfacial interaction between excipient of amorphous solid dispersions and IMC can provide valuable conclusions for comprehending the mutual interactions between host and guest in amorphous solid dispersions and designing amorphous solid dispersions with better application performances.

In the present work, interfacial interactions of amorphous solid

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dispersions matrix of IMC established by polyvinyl pyrrolidone K30 (PVP) and polyethylene glycol 6000 (PEG) were studied through mainly concerning with interaction forces and wetting process. PEG is widely used as matrix for amorphous solid dispersions because of their low melting point, rapid solidification rate, capability of forming solid drug solutions, low toxicity and low costs (Bley et al., 2010). PVP with glass transition temperatures (110–180 °C) is one of amorphous polymers as the excipient of amorphous solid dispersions(Papadimitriou et al., 2012). Herein, raman spectroscopy and infrared spectroscopy of IMC, PVP, PEG, IMC-PVP and IMC-PEG were studied. Wetting property that measured by the contact angle of water can reflect the hydrophobicity at the surface of the tablets. Surface free energy, dispersion force and polar force of molecules were obtained from contact angle measurement via Owens-Wendt-Rabel-Kaelble method. It is believed that the combination of materials and techniques enables us to demonstrate and explain unexpected wetting behavior of amorphous solid dispersions, and the obtained findings are of high general potential interest for many systems. Far from revealing the dissolution mechanism of IMC-PEG and IMC-PVP, the present work focuses on the interfacial interaction of drug and polymer then closely correlates interaction forces, contract angle and drug dissolution, and thus making contribution for designing, analyzing and evaluating amorphous solid dispersions constructed by water-soluble polymers.

2. Materials and methods

2.1. Materials

The PVP K30 (purity ≥ 99%), PEG 6000 (purity ≥ 99%) and anhydrous ethanol with analytical degree were purchased from Bodi Co. Ltd. (Tianjing, China). IMC was purchased from Melone Pharmaceutical Co. Ltd. (Dalian, China). Deionized water was used to prepare dissolution medium.

2.2. Synthesis of IMC-PVP and IMC-PEG

Amorphous solid dispersions of IMC-PVP and IMC-PEG were prepared by the solvent evaporation method as follows. 200 mg IMC and 1 g excipient were respectively dissolved in anhydrous ethanol, and IMC solution was poured into excipient solution under stirring (80 °C) until the solvents were all evaporated. The obtained amorphous solid dispersions were stored at − 20 °C refrigerator for 30 min. Finally, the amorphous solid dispersions were dried under vacuum at 40 °C, milled and sieved with particle size fractions 60 mesh.

2.3. Infrared spectroscopy (IR)

IR spectra of IMC, PVP, PEG, IMC-PVP and IMC-PEG were collected on an IR spectrometer (Spectrum 1000, Perkin Elmer, USA). The IR spectra, in absorbance mode, were obtained in the spectral region from 400 to 4000 cm^{-1}.

2.4. Raman spectroscopy

The solid state of the sample surface was analyzed in situ through a quartz sight window using a raman spectrometer (inVia Laser Micro Raman Spectroscopy, Renishaw PLC) equipped with a thermoelectrically cooled CCD detector and a fibre optic probe. The measurements were carried out at room temperature using a 500 mW laser source with a wavelength of 785 nm.

2.5. X-ray photoelectron spectra (XPS)

XPS was measured on a ESCALAB250 (Thermo VG, USA) with pass energy of 50.0 eV and energy step size of 0.05 eV. Quantification and curve fitting were performed using XPSPEAK4.1 based on elemental sensitivity factors supplied by the manufacturer.

2.6. Molecular modeling

Chemical structures of drug and exicipient were drawn by Marvin sketch software. The 3D structures of PVP and PEG were created by optimizing the structural minimization and the structural dynamics with the Sybyl 6.9.1 software package (Tripos Associates: St. Louis, MO, 2003). The determined parameters consisted of 0.005 energy change (kcal/mol), 10,000 max iterations and 0.005 kcal/(mol × A) energy change. The interactions between drug and polymers were studied using molecular docking using AutoDock 4.0 software (Liu et al., 2017). The results of molecular docking were analyzed by Discovery Studio 4.0 to comprehend the binding interactions between drug and polymers, and observe the receptor surfaces and get the lowest energy conformations.

2.7. Wetting property measurement

The contact angle of samples was studied using automatic contact angle meter model JCY series (Shanghai, China). Briefly, 200 mg sample was weighed and compressed using a circular stainless steel punch and die assembly (diameter 13 mm) in a infrared tablet press (dwell time for 10 s and pressure of 10^9 Pa). A drop of deionzed water (2 μL) was put on the compressed plate and the measurement of contact angle started in dynamic mode. Images were taken every 1 min for at least 100 min. Herein, tangent method was employed to calculate the contact angle of samples. Using the same working process, hexadecane instead of deionized water was dropped onto the surface of tables. With the obtained contact angle data of deionized water and hexadecane, surface free energy, dispersion force and polar force of molecules were calculated using Owens-Wendt-Rabel-Kaelble method.

2.8. Optical microscopy

To vividly present the wetting behavior of amorphous solid dispersions, optical microscopy (Nikon, China) was applied for observing IMC, PVP, PEG, IMC-PVP and IMC-PEG. After the scanning of these samples, one drop of deionized water (40 μL) was added onto their surface to give further observation. The magnification time was 15 × 10.

2.9. Scanning electron microscopy (SEM)

SEM was obtained with emission scanning electron microscope (JSM-6010, Japan) to analyze surface morphology of samples.

2.10. In vitro dissolution

In vitro dissolution experiment was carried out using USP paddle method (100 rpm, 37 °C) with a ZRD6-B dissolution tester (Shanghai Huanghai Medicament Test Instrument Factory, China). Samples were exposed to 250 mL enzyme-free simulated intestinal fluid (pH 6.8) prepared by dissolving potassium dihydrogen phosphate in deionized water and adjusting the pH with 1 M sodium hydroxide solution. At predetermined time intervals, 5 mL dissolution medium was withdrawn from the release medium and then an equivalent amount of fresh medium was added to maintain a constant dissolution volume. The withdrawn dissolution medium was administered through 0.45 μm microporous membrane then analyzed using UV-1750 (Shimadzu, Japan) at the wavelength of 320 nm.