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Amorphization of pharmaceutical compound by co-precipitation using supercritical anti-solvent (SAS) process (Part I)

Ron Tau Yee Lim[a,*], Wai Kiong Ng[a], Reginald B.H. Tan[a,b,**]

[a] Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore
[b] Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 119260, Singapore

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ABSTRACT

The aim of this work is to investigate the feasibility of using supercritical anti-solvent (SAS) co-precipitation process to influence the crystallinity or amorphous character of a crystalline non-steroidal anti-inflammatory drug (NSAID), indomethacin (IDMC) for solubility enhancement. Co-precipitations of IDMC and the water-soluble polymer excipient poly(vinylpyrrolidone) (PVP) have been prepared by SAS. The SAS co-precipitates with drug to polymer ratios of 85:15, 50:50 and 20:80 were generated using supercritical carbon dioxide as anti-solvent. The untreated and SAS powders (before and after storage) were characterised using scanning electron microscopy (SEM, morphology), powder X-ray diffractometry (PXRD, crystallinity), USP dissolution tester and thermogravimetric analysis. In addition, stability stress tests on SAS co-precipitates on open pans were carried out at 75% RH and room temperature or 40 °C in order to evaluate their physical stability. SAS co-precipitates with PVP contents more than 50 wt.% were X-ray amorphous and remained stable after 7 months storage at 75% RH and room temperature or 40 °C. It was demonstrated that the drug to polymer ratio influenced amorphous content of the SAS co-precipitates. By using different polymer ratios, the morphologies of a drug–polymer composite can be varied. TGA analyses revealed that the composition of SAS co-precipitates were consistent with the experimentally designed composition. Amorphous form of IDMC produced by SAS has improved dissolution properties as compared to the crystalline form. This form is also stable under stress test conditions compared as with spray-dried amorphous indomethacin. It is suggested that PVP excipient could be a suitable "amorphous inducing and stabilizing" agent for SAS process.

1. Introduction

Recently, the increase in the number of newly discovered poorly water-soluble drug candidates has heightened the interest in developing novel methods to improve aqueous-solubility. A new approach using supercritical fluids (SCF) for particle design of pharmaceutical materials is being actively pursued due to its major advantages over conventional pharmaceutical processing such as high purity of products, ability to control particle size and narrow particle size distribution, single-step process and free from residual solvent. Besides that, carbon dioxide is commonly used as the SCF for pharmaceutical materials processing due to its relatively mild critical pressure and temperature, non-toxic, relatively inert, non-flammable, and recyclable. Besides these advantages, one major challenge is to improve bioavailability and stability of poorly water-soluble active pharmaceutical ingredient (API) using supercritical fluids particle design technology [1]. In cases where low solubility limits absorption, the amorphous form may have an advantage in improving dissolution properties. There are a number of different methods to generate amorphous drug substances such as solvent deposition [2], co-grinding [3], melt extrusion [4], spray drying [5], melt quenching [6] and melt adsorption [7]. However, some of these applications may be difficult due to the thermal and deposition instability of drug during melting, which often poses a major problem [8,9]. Hancock and Parks [10] reported that the experimental solubilities of amorphous solids are at least 2–4 times greater than their crystalline counterparts. However, the improvement of these solubilities comes at the cost of decreased physical and chemical stability as compared to the crystalline counterpart. One of the possible methods to enhance physical stability of amorphous drug is through mixing the drug with a polymer at the molecular level [11–20].

Therefore, the dissolution rate of poorly water-soluble drug can be improved by dispersing it in a water-soluble biocompatible carrier such as poly(vinylpyrrolidone), polyethylene glycol, hydroxyl

* Corresponding author. Tel.: +65 67963867; fax: +65 63166183.
** Corresponding author at: Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore. Tel.: +65 67963841; fax: +65 63166183.
E-mail addresses: lim_tau_yee@ices.a-star.edu.sg (R.T.Y. Lim), reginald_tan@ices.a-star.edu.sg (R.B.H. Tan).

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propyl methyl cellulose, etc., which inhibit the crystallisation of the drug [21]. This approach leads to composite particle formation such as those obtained from solid solution and dispersion technologies for drug substances [22–26]. The effect of a polymer on the recrystallisation rate of amorphous substances is generally expressed in terms of properties of the metastable amorphous form such as molecular mobility, glass transition temperature (T_g) and the interactions arising between the drug and the polymer. Substances with higher entropy and enthalpy than the steady crystalline form, such as the amorphous or polymorphic forms can be obtained from these technologies by modifying the physical structure of the crystals. The amorphous state of drug can be stabilized by dissolving the drug into the polymer matrix at molecular level and restricting the drug molecules mobility thus hindering the recrystallisation process.

Gong et al. [27] successfully co-formulated of indomethacin and poly(vinylpyrrolidone) particles using solvent-free supercritical fluid technique. The X-ray amorphous products were obtained at relatively high PVP weight fractions of 0.8 and above. Deepak and Bogner [3] used co-grinding to obtain amorphous samples of indomethacin and neusilin (1:1, 1:4 and 1:5) mixtures. The amorphous products were stable over a period of 3 months at 40 °C/75% RH. Thus, the drug to polymer ratio plays a crucial role in the generation of co-formulation. A balance between drug and excipient in the final co-formulation should be attained to ensure sufficient shelf life and drug therapeutic efficacy. However, this optimisation requires more understanding on the drug–polymer thermodynamic system and the nature of amorphous character, which has not been well reported. Therefore, the aim of this research work is to investigate the effect of IDMC to PVP ratio on the crystallinity/amorphous properties, physical stability and dissolution rates of IDMC prepared using SAS.

2. Materials and methods

2.1. Materials

γ-Indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid), IDMC (Fluka) and poly(vinylpyrrolidone), PVP (molecular weight 360,000, Sigma) were used as received. IDMC, a poorly water soluble and non-steroidal anti-inflammatory drug (NSAID), which is classified as class II drugs in Biopharmaceutical Classification System (BCS) has low bioavailability and high permeability. IDMC is used as a painkiller and treating inflammatory conditions such as arthritis, osteoarthritis, alkylosing spondylitis and other disorders. Indomethacin existed in two known polymorphic forms of α and γ-indomethacin. The γ-phase constituting the monotropic system and is the thermodynamically more stable form than α-phase [28]. The melting point of the form is 155 °C with a heat of fusion of 91 J/g, whereas the γ form melts at 161 °C with a heat of fusion of 110 J/g [29]. The decomposition temperature of IDMC is 220 °C [29]. PVP (amorphous polymer) is a water-soluble, hydrophilic and hygroscopic polymer made from the monomer N-vinylpyrrolidone. Besides that, PVP also possesses chemical and biological inertness, low toxicity, high media compatibility, cross-linkable flexibility and other unique properties. The chemical structures of IDMC and the PVP repeating unit are shown in Fig. 1. Carbon dioxide 99.95% (SOXAL) purity was used as an anti-solvent for SAS process. Mixtures of IDMC and PVP at various weight ratios of 85:15, 50:50 and 20:80 were prepared by dissolving it into a mix-solvent containing reagent grade of acetone and dichloromethane. All the various weight ratios of IDMC and PVP have similar IDMC concentration of 12 mg/mL. The composition of mix-solvent is 80 and 20 vol.% of acetone and dichloromethane, respectively. All SAS co-precipitations processes were conducted

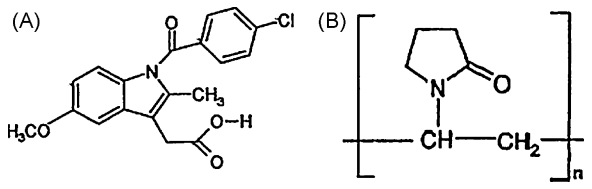

Fig. 1. (A) Indomethacin chemical structure; (B) poly(vinylpyrrolidone) repeating unit.

at 85 bar and 35 °C. Similar compositions of physically blended (PB) IDMC-PVPs were also prepared using Turbula T2F shaker-mixer at 49 rpm for 1 h. Besides that, spray-dried indomethacin (SD IDMC) was also prepared at 78 °C using BÜCHI Mini Spray Dryer from an IDMC-ethanol solution.

2.2. SAS experimental set-up and procedure

An SAS apparatus (model: SAS 50, Thar Technologies Co., USA) was used to generate different ratios of SAS IDMC-PVP co-precipitates. Pure IDMC and PVP were also generated using SAS process. Fig. 2 shows the schematic diagram of Thar SAS system using supercritical carbon dioxide (CO_2) as anti-solvent. Firstly, the CO_2 (1) was cooled down with a bath cooler (3) operating at 5 °C to assure liquid state in the pump. The liquefied CO_2 was then pumped into precipitation vessel (10) (500 mL vessel, 54 mm internal diameter and 218 mm internal height) using a high-pressure pump (11) through the CO_2 spray nozzle (16) (100 μm stainless steel orifice), to fill up the precipitation vessel. The flow-rate of CO_2 was set at 60 g/min. The CO_2 was heated using pre-heater (6) before entering the precipitation vessel. The pressure (85 bar) and temperature (35 °C) in precipitation vessel was controlled using an automatic back-pressure regulator, ABPR (13) and a temperature controller to regulate pre-specified heat to the heating jacket (8), respectively. Once the steady state was established, the solution pump (11) was switched on and sprayed the solution of drug and polymer (15) into the precipitation vessel through the solution spray nozzle (9) (100 μm stainless steel orifice). The flow-rate of the solution pump was set at 1 mL/min and approximately 50–80 mL of solution of drug and polymer was sprayed into the precipitation vessel. Rapid mixing between the two media and the fast diffusion of supercritical CO_2 into the drug solvent produces a supersaturated solution and causes the drug to precipitate as micronised particles. Once sufficient powders were collected in the metal frit (5), the solution pump was switched off and supercritical CO_2 was continuously pumped into the precipitation vessel to wash-up the remaining

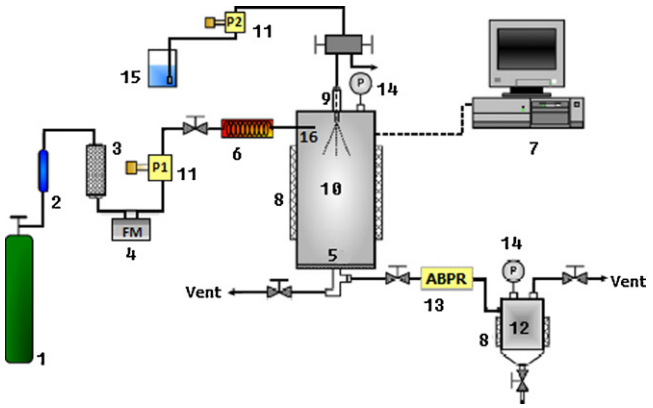

Fig. 2. Schematic diagram of a Thar SAS laboratory apparatus for co-precipitation. (1) CO_2 cylinder; (2) filter; (3) cooler; (4) mass flow meter; (5) metal frit; (6) pre-heater; (7) computer; (8) heating jackets; (9) solvent nozzle; (10) precipitator vessel; (11) high-pressure pumps; (12) separator; (13) automatic back-pressure regulator (ABPR); (14) pressure gauges; (15) drug solution; (16) CO_2 nozzle.