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One-step continuous extrusion process for the manufacturing of solid dispersions

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ABSTRACT

The purpose of this study was to evaluate the performance of synthetic magnesium aluminometasilicate (MAS) as a novel inorganic carrier in hot melt extrusion (HME) processing of indomethacin (IND) for the development of solid dispersions. A continuous extrusion process at various IND/excipient blend ratios (20%, 30% and 40%) was performed using a twin-screw extruder. Physicochemical characterization carried out by SEM, DSC, and XRPD demonstrated the presence of IND in amorphous nature within the porous network of the inorganic material for all extruded formulations. Further, AFM and FTIR studies revealed a single-phase amorphous system and intermolecular H-bonding formation. The IND/MAS extrudates showed enhanced INM dissolution rates within 100% been released within 1 h. Stability studies under accelerated conditions (40 °C, RH 75%) showed that MAS retained the physical stability of the amorphous solid dispersions even at high drug loadings for 12 months.

1. Introduction

The increasing number of new lead compounds that fail out in the discovery pipeline due to their poor water solubility is considered one of the major challenges in pharmaceutical formulation development. Therefore, there is a growing interest to improve the aqueous solubility and thus the oral bioavailability of those poorly water-soluble drugs for the development of oral dosage forms (Maniruzzaman et al., 2012). Several processing techniques have been utilized to improve drug solubility such as size reduction, hot spin mixing (Srinarong et al., 2011), spray drying (Alam et al., 2012; Jang et al., 2013), co-evaporation or co-precipitation (Kushida and Gotoda, 2013), freeze-drying (He et al., 2011), supercritical fluid processing (SFP) (Gong et al., 2005) and recently hot-melt extrusion (HME) (Maniruzzaman et al., 2013a,b). HME has been used as a processing technology in order to enhance the dissolution rates of poorly soluble drugs by producing solid dispersions. It is a solvent free, dust-free, environmentally friendly, easy to scale up and can be used as a continuous manufacturing process. HME has demonstrated its processing capability to develop various solid dosage forms such as pellets capsules, films or tablets (Maniruzzaman et al., 2013b; Repka et al., 2008, 2012; Gryczke et al., 2011; Lang et al., 2014). Generally, the high shear force generated inside the extruder barrel and the optimised processing parameters (*e.g.*, screw speed, feed rate, temperatures) during the HME process, are applied to overcome the crystal lattice energy of crystalline drugs and soften the carrier matrices. Up to date, most of these studies investigated the use of hydrophilic polymers or lipids as carrier matrices to develop solid dispersions (Maniruzzaman et al., 2013b; Repka et al., 2012).

The use of inorganic excipients (Gupta et al., 2002) as drug carries for increase dissolution rates of poorly water-soluble drugs is an attractive approach which can provide a new insight into pharmaceutical research and product development.

Bahl and Bonger (2006) reported the effects of magnesium aluminometasilicate (MAS) as a novel inorganic excipient on the increase of amophicity of indomethacin (BCS class II drug) in a mechanical ball milling process and thus enhancing its dissolution rates. Later on the same group reported a follow up study evaluating the solubility and dissolution profiles of indomethacin (both crystalline and amorphous state) in the presence of MAS as an inorganic carrier (Bahl and Bogner, 2008) via a ball milling process. The presence of silicic acid and Mg^{2+}/Al^{3+} ions, from the MAS molecule, in the dissolution media was found to cause the

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increase in the concentration of indomethacin and enhance its *in vitro* dissolution rates.

Maclean et al. (2011) proposed a scalable process to form a Sulindac-MAS amorphous drug complex using a twin screw granulation approach (Maclean et al., 2011). The dissolution properties of the resulting melt extruded material was improved while maintaining similar physical stability as those manufactured in ball milling.

MAS is an amorphous magnesium aluminometasilicate with a high specific surface area (300 m^2/g) (Fuji Chemical Industry Co., Ltd., 2015). Like many silicates, MAS generates different silanol types (*e.g.* free, germinal or associated) in contact with water, which make it a potential proton donor as well as a proton acceptor. MAS also presents exceptional excipients properties such as high flowability, high surface area, porous, thermal and mechanical stability for improved API delivery and the quality of pharmaceutical dosage forms. Indomethacin is a BCS class II drug with low solubility and high permeability which has been previously processed by HME for the development of polymeric solid dispersion either in amorphous state or molecularly dispersed (Maniruzzaman et al., 2013a,b; Chokshi et al., 2008).

The aim of the current study was to utilize inorganic excipients as drug carriers for the manufacturing of solid dispersions of water insoluble drugs with increase dissolution rates. HME was used a continuous one step extrusion process of drug—inorganic excipient blends at various IND loadings.

2. Materials and method

2.1. Materials

Indomethacin (≥98%) was purchased from Tokio Chemical Industries (Belgium) and magnesium aluminometasilicate (MAS-Neusilin® US2) (≥99%) was kindly donated by Fuji Chemical Industries Co., Ltd. (Japan). All solvents used were of analytical grade and used as received.

2.2. Hot-melt extrusion processing

All prepared binary mixtures were extruded without the die at temperatures varying form 170 to 200 °C to find the suitable extrusion temperatures. The extrusion was conducted in a twin screw (co-rotating) extruder with an L/D ratio 40:1 (ThermoFisher, Germany). The temperatures profiles were finally optimized using 50/100/180/180/180/180/ 180/180/180/180/25 °C (feeder—die) with a screw speed of 100 rpm and the feed rate of 1 kg/h. The feeding was optimized using a volumetric feeder equipped with single screw (Brabender, Germany). The temperatures, screw speed and the torque forces were recorded for each processed batch. Three different formulations with IND/MAS 20/80, 30/70 and 40/60 (%, w/w) were used for extrusion in order to obtain the final extrudates as free flowing granuless. The specific ratios of drug/excipients were chosen based on the dose of marketed indomethacin. Moreover a wide range of the drug loadings from 20 to 40% w/w ratios was investigated in order to develop amorphous solid dispersions and thus enhancing the dissolution of poorly soluble drug. No additional down streaming processing was required to micronize the particle size of the extrudates.

2.3. Residence time distribution and mean residence time measurement

The residence time (t) distribution (RTD) was measured by adding 0.5 g of Indigo Carmine (FDA approved food colorant with melting point >300 °C) pigment as a tracer to the hopper of the feeding section at a given time T_0. The color concentration of the

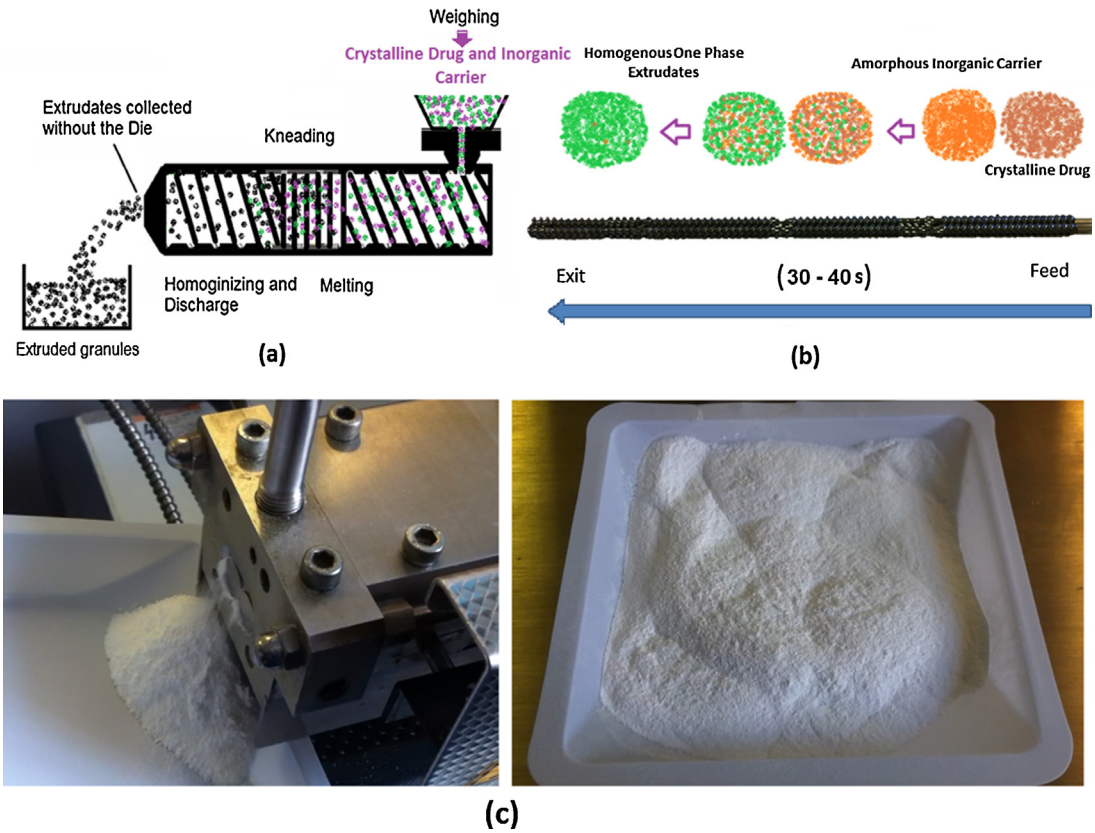

Fig. 1. (a) Schematic diagram of HME processing; (b) steps involved to manufacture extruded granules; (c) collected granules.