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A quality by design (QbD) twin—Screw extrusion wet granulation approach for processing water insoluble drugs

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ABSTRACT

In this study, a Quality by Design (QbD) approach was used to identify the effect of formulation parameters in a twin screw wet extrusion granulation process for the manufacturing of ibuprofen (IBU) granules with increased dissolution rates. A fractional factorial Design of Experiment (DoE) was used to investigate the effect of the excipient composition, binder amount and liquid to solid (L/S) ratio (independent variables) on drug dissolution rates, median particle size diameter and specific surface area (dependent variables). The intra-granular addition of the binder in inorganic/polymer blends processed with ethanol as granulating liquids facilitated the formation of granules at various particle sizes. DoE regression analysis showed that all formulation parameters affect the dependent variables significantly. The enhanced dissolution rates were attributed not only to the IBU particle size reduction and adsorption in the porous inorganic network but also to the high specific surface area of the produced granules. Dynamic vapour sorption showed increased water absorption for granules with small particle size distribution and high specific surface area.

1. Introduction

In the recent years twin–screw extrusion granulation (TSG) has attracted significant interest for the development of a variety of oral solid dosage forms such as granules, tablets or capsules in a continuous manufacturing manner. TSG approaches have been introduced as an alternative approach for the passage from batch processing to continuous manufacturing in the pharmaceutical industry. Although there are several reported studies, extrusion granulation is still in its infancy and further work is required to fully understand the technology (Schmidt et al., 2016). In a recent study, Thompson et al. highlighted the influence of various processing and formulation parameters on the granulation process. According to Thompson et al., and Djuric et al., scaling up of extrusion granulation is not a straightforward exercise and the mechanisms within the process need to be better understood (Thompson, 2015; Djuric et al., 2009).

The two major extrusion granulation approaches are a) wet granulation where the granulating liquid, with or without the addition of binders, is pumped into the screw zones and b) hot melt granulation which uses a molten binder to effectively bind the drug and the polymers (Weatherley et al., 2013). Both process can effectively manufacture high quality granules for immediate or sustained drug release, however, both processes also present a number of drawbacks. For example, wet granulation requires a drying step for water removal that is time consuming while hot granulation uses relatively high barrel temperatures varying from 60 to 100 °C.

An in-depth study was presented by Vercruysse et al., using a six-segmented fluid bed dryer of the ConsiGma™-25 system comprising of a continuous twin screw granulation and drying system (Vercruysse et al., 2015a). By running the system for 1 h the authors evaluated the effect of process outcomes, granule properties and tablet quality attributes. The torque and barrel wall temperatures were stabilized after 30 min performance while the tablet properties were adequate when comparing two ConsiGma systems (−1 and −25). Other studies have highlighted the impact of screw configuration on the particle size distribution, where conveying elements produced wide multimodal size distributions, while kneading elements have found to narrow the size of agglomerates (Vercruysse et al., 2015b; Meng et al., 2016). The delivery of the binder in the powder blend or in the

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granulating liquid has a tremendous effect on the obtained granule quality (Saleh et al., 2015; Batra et al., 2017). The incorporation of binders, which are blended in the powder mix, resulted in longer residence times and higher torque, but also produced narrower particle size distribution, spherical granules and better binder distribution. In contrast, Fonteyne et al. demonstrated that excellent binder distribution can be obtained by both when the binder is added in the dry blend or when it is added within the granulation liquid (Fonteyne et al., 2014). In the case of melt granulation, low melting binders create stronger granules and the binder molecular weight appeared to have no effect in the process (Weatherley et al., 2013). More recently the use of a foamed binder solution led to the formation of more uniform wetted mass and larger granule growth (Rocca et al., 2015; Thompson et al., 2012).

Meier et al. (2016) showed that the feeder performance in conjunction to the screw design influences the granule quality for highly drug loaded formulations and the obtained granule particle size requires detailed knowledge of the feeding systems (Meier et al., 2016). The formulation composition is an aspect that clearly should be taken in account (Meier et al., 2015; Keen et al., 2015; Vanhoorne et al., 2016) where binary or ternary premix blends affect the granule quality as well as the drug dissolution rates.

In order to understand the granulation process and the mechanisms involved during material processing, in – line and off – line process analytical tools (PAT) have been implemented to provide valuable insights (Fonteyne et al., 2016; Monteyne et al., 2016a, 2016b; Kumar et al., 2014a, 2014b; Vercruysse et al., 2014; Chablani et al., 2011; Maniruzzaman et al., 2015). Near infrared (NIR) probes were used to measure the granules moisture content in comparison to Karl Fisher and loss of drying moisture measurements. In addition, NIR was used to understand the mixing and distribution of granulating liquid. The coupling of Raman mapping with twin – screw granulation provides information of the polymorph transitions and allows mapping of the drug distribution in the granular agglomerates. Similarly, the binder mixing efficiency and distribution was identified through hyperspectral coherent anti-Stokes Raman scattering (CARS) microscopy. The use of high-speed camera enabled also the visualization of the particle size distribution and shape in real time.

The purpose of the current study was to investigate the effect of formulation parameters such as excipient composition ratio, binder amount and L/S ratio on the granule formation of a water insoluble drug when processed with organic granulating liquids. Dry blends of inorganic excipients such as anhydrous dicalcium phosphate with a low molecular weight hydrohyxpropylmethyl cellulose (HPMC) grade were processed for first time with ethanolic granulating liquid.

2. Materials and methods

2.1. Materials

Ibuprofen (IBU) was purchased from FarmaShino Pharmaceuticals Co. Ltd., (Nanjing, China) and dibasic calcium phosphate anhydrous (DCPA, Fujicalin®, DCPA) was kindly donated by Fuji Chemical Industries Co., Ltd. (Japan). Hydroxypropyl methylcellulose based polymer Pharmacoat 603 (HPMC) was kindly donated by Shin Etsu, Japan. Polyethylyne glycole 2000 (PEG) and ethanol (95%, 190 proof) were purchased from Sigma Aldrich (Gillingham, UK). All solvents used were of analytical grade and used as received.

2.2. Twin screw granulation and DOE analysis

Extrusion granulation studies were conducted using a twin-screw extruder (EuroLab 16, Thermo Fisher, Duisburg, Germany) with a length/diameter (L/D) ratio of 40). A configuration with three kneading zones at 30°/40°/60°, 60° and 90° angles respectively was used for all the granulation trials. The IBU formulations were thoroughly mixed in a Turbula (TF2, Basel, Switzerland) mixer of 1 kg batches for 10 min each, prior to the extrusion process. During granulation, dry blends of the drug, polymer, inorganic carrier and the binder PEG were fed into the extruder with a volumetric feeder (Brabender, Duisburg, Germany) at 1 kg/h feed rate while the screw rate was set at 100 rpm under ambient temperature. A peristaltic pump, plunged in close proximity to the extruder's feeding opening, supplied the granulating liquid (ethanol) at a constant rate. The "as made" extruded granules were dried in an oven (Memmert UF30, UK) at 30 °C for 2 h then further micronized through a cutter mill (Retsch, Germany) with a 250 μm fitted mesh.

For the QbD approach a Design of Experiment (DoE) was introduced by using Fusion One software (DoE Fusion One™, California, USA). A response surface fractional factorial design ($2^3 + 3 = 11$) in randomized order with three centre points was designed with three independent and three dependant variables. The drug loading was kept constant (40%) where the DCPA/Polymer ratio (0.33–2.0), binder amount (5–12%) and L/S ratio (0.25–4.0) were set as independent variable. The drug release rate, the median particle size distribution (D50) and specific surface area (SSA) were defined as the dependant variables.

2.3. Particle size analysis

The particle size distribution of the extruded granules was determined using a Mastersizer 2000 laser diffraction analyser (Malvern Instruments, UK) with a dry powder sample dispersion accessory (Scirocco 2000). Samples were processed with a pressure at 0.5 bar and a vibration feed rate of 50% in triplicate. The software analysis provided the d(10) d(50) and d(90) granular particle size values which are the geometric median particle size particle diameters at 10 and 90% of the cumulative volume distribution, respectively.

2.4. Scanning electron microscopy (SEM)

SEM images of the extruded IBU granules were captured using a cold-cathode field-emission gun scanning electron microscope (Hitachi SU8030 FEG-SEM, Tokyo, Japan) with 30 mm2 Ultra-Dry window and Noran 7 software. The samples were glued using

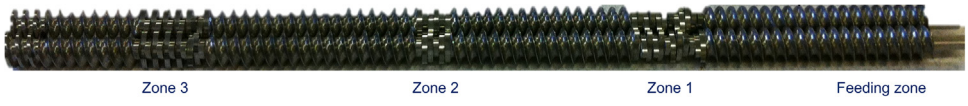

Fig. 1. Image of the twin – screw configuration used for the extrusion granulation process.