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Development and characterisation of semi-crystalline composite granules: The effect of particle chemistry and the electrostatic charging

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ABSTRACT

This study investigated the surface of semi-crystalline composite granules produced via a novel mechano-chemical process and assessed the effect of electrostatic charging. Ibuprofen (IBU), a model drug with low solubility and known associated processing challenges was loaded in composite granules to improve its processibility and dissolution rates. Synthetic amorphous mesoporous magnesium alumina metasilicate (MAS) was co-processed with hydrophilic HPMC polymer in the presence of polyethylene glycol 2000 (PEG) and deionised water. The solid state analyses conducted by scanning electron microscopy (SEM), X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) revealed the existence of semi-crystalline IBU in the complex composite structures. Dynamic vapour sorption (DVS) study showed the water sorption and desorption profiles of the manufactured composite granules as well as the effect of water on the solid-state stability of IBU in various formulations. Advanced surface analysis conducted via energy dispersive X-ray (EDS) revealed homogenous distribution of the drug/excipients on the surface of the granules while atomic force microscopy (AFM) complemented the findings. The electrostatic charge analysis showed variable charge property which is affected by the size of the particles/granules. As expected, the *in vitro* dissolution study showed about 5 fold increase in the release rates of IBU compared to that of the bulk drug. The mechanochemical processing has been demonstrated as an efficient technique to develop semi-crystalline composite granules with enhanced dissolution rates of water insoluble drugs.

1. Introduction

Approximately 40% of the recent medicinal lead compounds met in the discovery pipeline are considered hydrophobic that leads to a low dissolution and poor bioavailability [1]. Such compounds mainly belong to Biopharmaceutical Classification Systems (BCS) class II which are high permeable with limited absorption or solubility. Therefore, the dissolution is the rate-limiting step in drug absorption of this class [1,2].

The Noyes–Whitney equation reveals a direct link of the increase in dissolution rate with that of surface area [3,4]. Generally, an increase in the surface area occurs when the particle size of the drug is reduced thus the dissolution rate is enhanced. Therefore, micronisation or reduction of the particle size of drug candidates may prove an efficient approach to enhance its dissolution rate. However, in the processing of poorly water-soluble drug, many associated challenges may have to be overcome as not only may the solubility of the drug influence its bioavailability but also their solid state properties. The solid state properties of the drug may be influenced by the way in which they are developed and formulated [4–8]. Different complementary pharmaceutical technologies/methods have been employed to overcome such processing issues of water insoluble drugs such as the use of pharmaceutical grade polymers e.g. poly(ethylene glycol) (PEG) and starch as meltable polymer excipients [9]. These polymers alone or when co-processed with other excipients may improve the solubility and dissolution profile of the drugs by means of resulting in the formation of composites. These composite forming materials ease the preparation and processing that are commercially viable and scalable products [9,10]. In this study, we investigate the manufacturing of composite granules that are suitable to process a low

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melting point, sticky, poorly soluble drug.

Granulation process is highly and most commonly used by the pharmaceutical manufacturers to manufacture oral pharmaceutical products. From the outset of the pharmaceutical implementation of granulation process, it has mainly been improved using contemporary pharmaceutical technologies such as high shear/fluid bed granulations, in batch manufacturing mode [11,12]. During the mechanical granulations process, the manufactured granules are prone to triboelectric charging due to the collision of the particles with the container walls and with each other [13,14]. This generated particle charging can cause severe problems in the intermediate steps of the pharmaceutical product manufacture by affecting powder flow and dose uniformity [15,16]. Therefore, triboelectrification can be used as a way of manipulating the charge of their final product of the granules manufacture via a granulations approach.

To the best of our knowledge, most of the previously reported studies primarily emphasised on the process optimization. None of them reported the granulation technology to manufacture composite granules with detailed particle chemistry in order to enhance the dissolutions of water insoluble drugs (e.g. ibuprofen). We investigate the effect of both formulation composition and the processing techniques on the dissolution rates of a poorly water soluble drug with a particular emphasis on the particle chemistry. Neusilin is an amorphous mesoporous magnesium aluminometasilicate (MAS) which has relatively high specific surface area (300 m^2/g) [17–19]. MAS also exhibits high flowability, mechanical stability and thermal properties which helps the API processing to develop dosage forms. On the other hand, ibuprofen (IBU) is a nonsteroidal anti-inflammatory drug with a relatively low melting temperature (77 °C) and poor water solubility. Being difficult to compact IBU has a soapy bitter and burning taste and can be used as an ideal candidate to assess processing method without compromising the dissolution rates [20].

In this study, we investigate the composition, processing, and performance properties of a model ternary composite system using IBU with known associated formulation challenges. The role of MAS as an alternative granulation carrier has also been explored and supported with physicochemical characterisation data. A novel triboelectrification strategy has also been studied to assess the impact of the particle charging on the performance and physical properties of the manufactured composite granules.

2. Materials and methods

2.1. Materials

Ibuprofen (IBU) and polyethylene glycol 2000 (PEG) were bought from Sigma-Aldrich (Gillingham, UK). Neusilin US2 (magnesium aluminometasilicate -MAS) was obtained from Fuji Chemical (Japan). Hydrophilic polymeric carrier, hydroxy propyl methyl cellulose polymer K4 (HPMC) was obtained from Colorcon Ltd, (Dartford, UK) as a gift. All solvents utilised in HPLC were of HPLC grade only while the rest of solvents used were of analytical grade.

2.2. Preparation of the composite granules

Various drug/MAS/PEG 2000 compositions (10 g) were mixed thoroughly (Table 1) in a mortar and pestle with the slow addition of granulating liquid (20% w/w) prior to mixing in a Turbula TF2 mixture (Basel, Switzerland) for 10 min. The granulating liquid used in this study is deionised water. The granules were not dried prior to mixing in the Turbula mixer. The obtained mixture of drug-loaded formulations were then subject to grinding (Ball Mill, Retsch, Germany) at 400 rpm with 8 balls for 5 min followed by granulations using Erweka AR403 granulator (Heusenstamm, Germany) with oscillating rotor set at 100 rpm and 0.315 mm sieve. Physical blends of the drug and excipients were made for comparison purpose which were not subject to the mechanochemical processing. All collected composite granules were then further sieved manually to obtain an optimum particle size threshold d(50) below 250 μm.

2.3. Particle size analysis

The particle size of all manufactured composite granules was analysed via a laser diffraction method (Mastersizer 2000, Malvern Instruments, UK). Scirocco 2000 as a dry powder sample dispersion accessory was integrated with the particle sizer. All samples were run in triplicate while pressure was set 2 bars and feed rate at 50%. All data acquisitions, interpretations and calculations were undertaken by Mastersizer 2000 software as well as the d(50) which is the geometric median particle size and the d(10) and d(90) which are the particle diameters at 10% and 90% of the cumulative volume distribution, respectively. The span referred to the width of the distribution relative to the d(50) was determined via equation (1).

$$Span = \frac{[d_{(90)} - d_{(10)}]}{d_{(50)}} \quad (1)$$

2.4. Atomic force microscopy (AFM)

An easyscan 2 (nanosurf, Switzerland) machine was used to take AFM photographs on tapping mode by using tap 190Al-G cantilevers (BudgetSensors, Sofia, Bulgaria). The intermittent force between the oscillated tip and the substrate were kept to minimum by balancing the drive amplitude and the relative set point. SPIP software (Image Metrology, Hørsholm, Denmark) was utilised to analyse the images and for the data interpretations.

2.5. Scanning electron microscopy (SEM)/energy dispersive X-Ray (EDS) analysis

SEM images were captured using a cold-cathode field-emission gun scanning electron microscope (Hitachi SU8030 FEG-SEM, Japan) and Thermo-Noran (USA) EDX system with 30 mm^2 Ultra-Dry window and Noran 7 software. The samples were glued with a double-sided carbon adhesive tabs and coated with carbon (Edwards 306 high vacuum carbon evaporation) prior to the SEM/EDX analysis. The accelerating voltage was set at 8 kV. Principal components were extracted from the X-ray maps using Noran 7 COMPASS software. The particle distribution on the surface area was characterized on the basis of chemical composition and morphology by using XPhase.

Table 1
Formulation compositions of IBU (40% w/w) loaded composite granules.

Formulation	HPMC/MAS (% w/w)	PEG (% w/w)	d(10) (μm)	d(50) (μm)	d(90) (μm)	Span	SSA (m^2/g)	LoD (%)
IBU			25.20	70.10	195.10	2.43		
F1	35/15	10	35.13	150.00	265.10	2.6	0.09	1.78
F2	25/25	10	2.27	97.10	286.40	3.3	0.10	1.80
F3	15/35	10	54.15	140.60	258.40	1.5	0.06	2.01
F4	25/20	15	42.61	125.10	246.60	1.6	0.07	1.57