Powder Technology 292 (2016) 342–350

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

An assessment of triboelectrification effects on co-ground solid dispersions of carbamazepine

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ARTICLE INFO

Article history:
Received 24 August 2015
Received in revised form 3 February 2016
Accepted 5 February 2016
Available online 6 February 2016

Keywords:
Electrostatics
Solid dispersions
Triboelectrification
Carbamazepine
D-Glucosamine HCl
Polymorphism

ABSTRACT

One of strategies adopted to improve the dissolution rates of poorly soluble drugs is by co-grinding the drug with a hydrophilic carrier. However, the introduction of mechanical forces during the grinding process can lead to changes in the physicochemical characteristics as well as an increase in the surface free energy of the ground particles, which causes an alteration in the electrostatic properties of these particles. The solid state characteristics of glucosamine hydrochloride (GLU) and carbamazepine (CBZ) and their co-ground mixtures were studied using DSC, XRPD and SEM. These revealed that polymorphic transformations occurred due to the grinding process. The influence of grinding time on the triboelectrification properties of the formulations was also studied. Both pure CBZ and GLU powders were predominantly electro-positively charged and their charging properties increased with increasing grinding time. CBZ:GLU physical mixtures exhibited complicated bipolar charging behaviour, however, when subjected to grinding, these mixtures demonstrated mainly electronegative charge properties. The influence of both grinding time and CBZ content within CBZ:GLU mixtures was examined. The value of net-electronegative-charge density of CBZ:GLU mixtures was shown to increase with grinding time and/or when increasing the percentage proportion of CBZ up to 30% w:w. This study helps to provide information about the handling of these formulations and gives a formulator tools to ascertain appropriate ratios for handling and possible simultaneous dissolution improvements.

1. Introduction

The poor aqueous solubility of BCS Class II drugs and new chemical entities is a major problem being faced in pharmaceutical development. The solubility and dissolution rate of these drugs are important determinants of the rate and extent of their absorption from the gastrointestinal tract. In addition, for this class of drugs, dissolution rates are the rate limiting step for bioavailability, therefore enhancing the dissolution rate is crucial to achieving therapeutic blood concentrations. Several techniques have been explored to enhance the dissolution rate of poorly soluble drugs and they include particle size reduction [1], solid dispersion formation [2], complexation [3] and salt formation [4]. The particle size reduction method has been extensively used in attempts to improve the dissolution rate of poorly soluble drugs [5,6] because the reduction in particle size and the subsequent increase in surface area can enhance the dissolution rate and consequently the bioavailability of these pharmaceutical materials. This method is promising but still has some difficulties in its application.

Size reduction of pharmaceutical materials is often performed by a dry milling process, requiring a high energy input, and it has been reported that the strong mechanical forces required (such as grinding) may increase the surface free energy and cause distortion of the crystal lattice as well as reduce particle size [7]. In addition, grinding of hydrophobic drugs usually causes aggregation of drug particles, therefore size reduction by dry milling is limited to around 3 μm due to aggregation between particles at sub-micron diameters [8]. These aggregates have a reduced effective surface area available for dissolution. Size reduction in the nanometre range must be carried out by other techniques such as salt-assisted milling [9]. Recent research has explored particle size reduction to the submicron range by co-grinding with additives [10–13]. Co-grinding is economically and environmentally desirable as, unlike other techniques, it does not require toxic solvents [14] and sophisticated equipment [15].

Abbreviations: GLU, glucosamine hydrochloride; DSC, differential scanning calorimetry; XRPD, x-ray powder diffraction; BCS, biopharmaceutical classification system; CBZ, carbamazepine; SEM, scanning electron microscopy; RH, relative humidity; PSD, particle size distribution; PM, physical mixture.

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http://dx.doi.org/10.1016/j.powtec.2016.02.008
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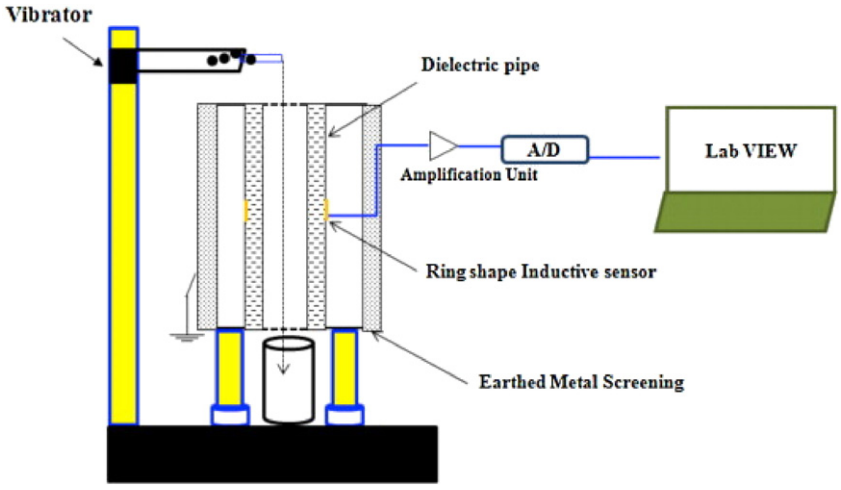

Fig. 1. Schematic of experimental setup used in the determination of the formulations charge.

Pharmaceutical powders usually have insulating properties with relatively small particle size and low bulk density and as such they are susceptible to triboelectric charging, especially during mechanical processing when particles collide with walls of containers and with each other [16,17]. In addition, particle charging can cause problems in the manufacture of formulations by affecting powder flow, reducing fill and dose uniformity [18,19]; for example particle charging may cause adhesion and deposition of particles to walls especially in the case of fine particles such as in dry powder inhalers [20,21]. Triboelectrification has been used to study the impact of the counter ion on flurbiprofen salts as a consideration during the preformulation process [22], reduce the charging of flurbiprofen (a drug with a high propensity for charging) in binary mixtures of cellulose ethers [23], ordered mixing [24] and recently as a way of manipulating the charge of their final product of solid dispersions using single solvents and binary mixtures of solvents [25].

Al-Hamidi et al., [2] explored the use of D-glucosamine HCl (GLU) as a potential excipient to improve the dissolution rate of poorly soluble drug by use of the co-grinding approach. They also investigated the effect of the order of grinding on dissolution and they found the co-grinding technique to significantly increase the dissolution rate of the poorly soluble drug carbamazepine (CBZ). However, they did not explore the handling issues which may potentially arise as a result of grinding. Given that the grinding process gives rise to charging and that particle triboelectrification plays an important role in powder processing, subsequently affecting the quality of formulations [16], the objectives of this study were to characterise the full charging profiles of pure CBZ and GLU and their co-ground mixtures. As Al-Hamidi et al. [2] reported GLU as a new carrier for improved dissolution behaviour for poorly soluble drugs, it is important to evaluate its effects on API handling. To the best of our knowledge, there is no work that has looked at the effects of duration of grinding on co-ground mixtures of the drug and carrier.

2. Materials and methods

2.1. Materials

Carbamazepine (CBZ) and D-(+)-glucosamine hydrochloride (GLU) were purchased from Sigma-Aldrich (UK). These materials were used as obtained from the supplier.

2.2. Preparation of physical mixtures of drug–carrier

Physical mixtures of CBZ:GLU (5 g in total) were prepared by mixing CBZ and GLU in a Turbula™ blender (Turbula, Basel, Switzerland) for 10 min. Different weight ratios of drug:carrier (1:1, 1:2 and 1:4 w/w) were prepared for comparison purposes. After mixing, the powders were stored in a screw-cap glass vial for one week at room temperature before use.

2.3. Preparation of co-ground mixtures of drug–carrier

Co-grinding of the formulations was conducted according to Al-Hamidi et al., [26,27]. Briefly, co-grinding of different ratios of drug to carrier (1:1, 1:2 and 1:4 w/w) was achieved using a ball mill (Pulverisette 6, Fritsch, Germany). The total amount of drug:carrier was kept constant for all formulations (20 g) during the co-grinding process. The volume of the mill chamber was 250 mL. Eight stainless steel balls, with diameter 20 mm, were used and occupied one third of the volume of the chamber. The vibration rate was 400 rpm. The samples (drug:carrier) were subjected to different grinding times (10, 30 and 60 min).

2.4. Scanning electron microscopy (SEM)

Electron micrographs of different samples were obtained using a scanning electron microscope (Leica Cambridge S360, UK) operating at 15 kV. The samples were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were recorded to study the morphology of the different samples.

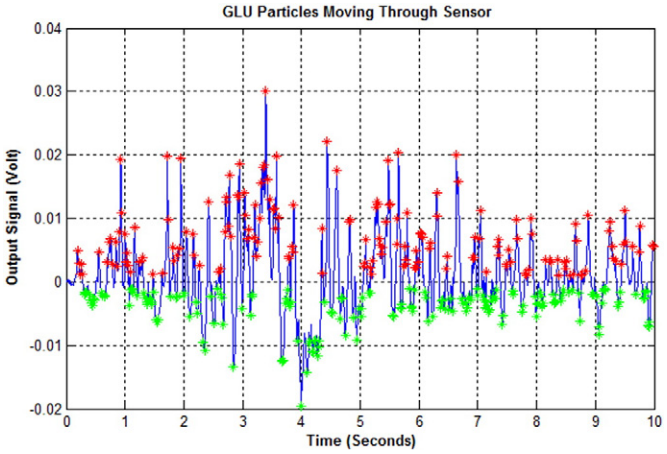

Fig. 2. A typical example of filtered data generated when GLU particles are travelling through the sensor.