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Research paper

Counter-intuitive enhancement in the dissolution of indomethacin with the incorporation of cohesive poorly water-soluble inorganic salt additives

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ABSTRACT

The objective of this work was to investigate the influence of various micronized poorly water-soluble inorganic materials on the dissolution and de-agglomeration behaviour of a micronized, poorly water-soluble model drug, indomethacin, from lactose interactive mixtures. Dissolution of indomethacin was studied using the USP paddle method and the data were modelled with multi-exponential equations using a nonlinear least squares algorithm in order to obtain key parameter estimates. The dispersion of indomethacin mixtures was measured by laser diffraction. The addition of aluminium hydroxide and calcium phosphate to binary mixtures of indomethacin counter-intuitively improved the dissolution rate of indomethacin due to significant increases in both the estimated initial concentration and dissolution rate constant of dispersed particles of indomethacin. While some enhancement was due to pH changes in the dissolution medium, the presence of these poorly water-soluble inorganic salts caused de-agglomeration. Average particle size distributions indicated that the presence of aluminium hydroxide within the matrix of indomethacin had reduced the agglomerate concentration whilst increasing the dispersed particle concentration. These findings provide the first evidence of the ability of poorly water-soluble inorganic salts to enhance the de-agglomeration and dissolution of micronized powders, potentially translating to improved bioavailability of poorly water-soluble drugs.

1. Introduction

Poor water solubility represents one of the major causes of drug candidate failure in pharmaceutical product pipelines, whereby more than one-third of drugs listed in the United States Pharmacopoeia are poorly water-soluble [1]. For compounds that are poorly soluble in water and show dissolution-limited absorption, incomplete oral bioavailability can result. Dissolution is maximized only when the drug is fully dispersed in the gastrointestinal fluids.

Particle size reduction is often used to generate micron or submicron-sized drug particles with increased surface area for more rapid dissolution in the gastrointestinal tract; however, such fine particles are cohesive and agglomerate since at such sizes, the van der Waals attraction generally exceeds gravitational detachment [2,3]. Due to a reduced surface area available for dissolution, agglomerates of poorly water-soluble drugs are difficult to disperse and can experience poor dissolution rates.

Formulation strategies have been developed to enhance the dissolution of cohesive poorly water-soluble micronized drugs that agglomerate. Creation of interactive mixtures, which theoretically consist of fine drug particles adhered onto coarse carriers, has contributed to formulation optimization in several ways. Firstly, this approach increases the homogeneity of low dose drugs [4] and also enhances the bulk flow characteristics. Secondly, interactive mixtures have been shown to contribute to the improvement of drug dissolution and bioavailability [5]. As the cohesive drug adheres onto the coarse carrier surface, agglomeration is reduced and a larger drug surface area is exposed to the dissolution medium. Hence, an improved dissolution rate is achieved. The use of water-soluble carriers may further enhance drug dissolution because they dissolve rapidly in the dissolution medium and increase the dispersion state of the micronized powders [6]. In addition, other strategies to reduce agglomeration and its effects during drug dissolution in interactive mixtures include the incorporation of surfactants [7–10], as well as using both lower concentrations of the drug [11–13] and smaller carriers [6,14]. The latter two strategies can give rise to increased carrier surface areas available to the drug, therefore resulting in greater dispersion.

The formulation strategies described rely on the drug particles being fully dispersed on the carrier surface. While this can happen in some instances, it is more likely that powder mixing processes result in complex mixtures of interactive units and agglomerates.

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Mixture particulate composition will depend on processing conditions, and drug and formulation properties. Thus, in reality, some other de-agglomeration mechanism will be required for complete powder dispersion in the dissolution medium.

In parallel to dissolution studies, research into the use of interactive mixtures for dry powder inhalers has revealed the importance of the structure of agglomerates in affecting the extent of drug aerosolization [15–17]. These studies demonstrated that the incorporation of micronized lactose and other micronized materials in lactose carrier-based interactive mixtures had a positive impact on the aerosolization efficiency of drugs through improved de-agglomeration. The resultant mixed agglomerates of micronized drug and micronized lactose (or micronized drug and other micronized materials) were proposed to have reduced tensile strength, as the dispersion of agglomerates was related to the tensile strength [3].

The tensile strength (σ) of agglomerates is dependent on the particle size, work of adhesion and packing fraction of the agglomerates. Many mathematical models have been used to define tensile strength and one of the equations is as follows [18]:

$$\sigma = \frac{15.6\phi^4 W}{d} \tag{1}$$

where ϕ is the packing fraction, W is the work of adhesion and d is the particle diameter.

As the particle size of a drug is confined by its functionality, the ability to modify the strength of agglomerates can be achieved by either manipulating the particle surface composition or morphology to change the work of adhesion, or by changing the packing fraction of the agglomerate by, for example, adding materials that will modify the agglomerate structure.

Previous studies have shown that the presence of micronized lactose increased the dissolution rate of drugs through an "agglomerate modifying" mechanism [19]. The increased de-agglomeration and dispersion was attributed to the open packing structure of mixed agglomerates that had formed. Unexpectedly, preliminary findings during our research demonstrated that the presence of micronized poorly water-soluble materials also increased the dissolution rate of drugs. It is hypothesized that these micronized inorganic salts could lead to the formation of mixed additive-drug agglomerates that more readily de-agglomerate than pure drug agglomerates alone. Therefore, the aim of this project was to systematically test the effect of micronized poorly water-soluble inorganic salts in enhancing the dissolution of a poorly water-soluble model drug, indomethacin.

2. Materials and methods

2.1. Materials

Micronized indomethacin, IMC (Sigma–Aldrich, USA), was employed as the model drug (D_{10} = 1.7 μm, D_{50} = 4.8 μm, D_{90} = 14.5 μm). Two lactose carriers were used including lactose-povidone granules (D_{10} = 12.8 μm, D_{50} = 95.6 μm, D_{90} = 233.3 μm) and lactose spray-dried for direct compression (D_{10} = 68.9 μm, D_{50} = 149.3 μm, D_{90} = 244.3 μm) (The Lactose Company of New Zealand, New Zealand). The cohesive poorly water-soluble excipients used as ternary components in the mixtures were inorganic salts, including: aluminium hydroxide (AH) (Merck, Germany) (D_{10} = 2.0 μm, D_{50} = 7.0 μm, D_{90} = 37.6 μm), barium sulphate (BS) (Riedel-deHaën, Germany) (D_{10} = 2.4 μm, D_{50} = 5.2 μm, D_{90} = 9.7 μm), dibasic calcium phosphate dihydrate (CP) (Mendell, USA) (D_{10} = 2.8 μm, D_{50} = 7.4 μm, D_{90} = 15.6 μm) and calcium sulphate dihydrate (CS) (Fluka, Switzerland) (D_{10} = 3.2 μm, D_{50} = 7.1 μm, D_{90} = 16.8 μm). These inorganic materials are commonly used pharmaceutical excipients in oral dosage formulations [20–25] and are generally regarded as being nontoxic following oral administration [26].

The media used for the dissolution studies included deionized water (Milli-Q water purification system, Millipore Corporation, USA), phosphate buffer pH 5.0 and acetate buffer pH 5.0 (British Pharmacopoeia, 2009). IMC has a pK_a of 4.5 [27,28], and its solubility will change significantly with change in pH. The pH condition of pH 5.0 was chosen to balance the ability to achieve a solubility which would provide sink conditions with analytical capability using ultraviolet (UV) analysis and discrimination for testing small differences in dissolution rate [29,30]. Note at pH 7.0, the rate of dissolution was very rapid due to the high solubility. The buffer solutions were prepared using deionized water, potassium dihydrogen phosphate (Merck, Germany), potassium hydroxide (Merck, Germany), sodium acetate trihydrate (Merck, Germany) and glacial acetic acid (Scharlab, Spain). Sodium lauryl sulphate (SLS) (Sigma, Australia) was added to the dissolution medium (0.1% w/v) to improve the wettability of IMC.

The following solvents were used as the dispersion media for the particle size measurements of the various materials: deionized water and 0.01% w/v SLS solution for IMC and all inorganic salts, and propan-2-ol (Merck, Australia) for lactose.

2.2. Particle size analysis of powders

Particle size distributions (PSD) of the raw materials were determined by laser diffraction using the Malvern Mastersizer S (Malvern Instruments Ltd., UK). A reverse Fourier lens with a 300 mm focal length and an active beam length of 2.4 mm was attached to a small volume dispersion cell (MSX1) containing a stirrer (set to half the maximum speed), in order to measure particle sizes ranging from 0.05 to 900 μm.

Specific presentations were created for each material analyzed and these included their refractive index (RI) values in order to account for the different optical characteristics of the particles and dispersing liquids listed in Section 2.1. Prior to performing particle size measurements, a slurry of each sample was first prepared and sonicated for 5 min. An adequate amount of each material was then added to 50 ml of the dispersion medium contained within the dispersion unit to achieve an obscuration range between 10% and 30%.

Analysis of micronized IMC and all inorganic excipients were determined in water and slurries of each sample were prepared using a few drops of 0.01% (w/v) SLS solution. The reference RIs for IMC, AH, BS, CP, CS and water were 1.74, 1.69, 1.64, 1.63, 1.60 and 1.33, respectively, with an estimated imaginary RI of 0.01 for all samples. Measurement of spray-dried lactose was performed using propan-2-ol as the dispersant with the reference RIs for lactose and propan-2-ol as 1.533 and 1.378, respectively, and an imaginary RI of 0.001. Drops of the dispersant were used to prepare a slurry of the lactose before addition to the dispersion unit.

Average PSDs were derived from five replicates for all samples and log-normal graphs of frequency by volume (%) versus particle size were then constructed. These were further characterized by the D_{10}, D_{50}, D_{90} cumulative particle undersize values and volume mean diameter (VMD).

2.3. Dispersion of mixtures by the Spraytec

To assess the extent of dispersion in air, *in situ*, real-time PSDs of the IMC mixtures were measured by laser diffraction using the Spraytec particle sizer (Malvern Instruments Ltd., UK), equipped with an inhalation cell attachment. Analysis was undertaken with a Rotahaler® inhaler device (GlaxoSmithKline, UK) at a flow rate of 60 l/min, calibrated with a TSI 4000 series flow meter (TSI Instru-