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Improving the de-agglomeration and dissolution of a poorly water soluble drug by decreasing the agglomerate strength of the cohesive powder

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ABSTRACT

Influence of ternary, poorly water-soluble components on the agglomerate strength of cohesive indomethacin mixtures during dissolution was studied to explore the relationship between agglomerate strength and extent of de-agglomeration and dissolution of indomethacin (Ind). Dissolution profiles of Ind from 20% Ind-lactose binary mixtures, and ternary mixtures containing additional dibasic calcium phosphate (1% or 10%; DCP), calcium sulphate (10%) and talc (10%) were determined. Agglomerate strength distributions were estimated by Monte Carlo simulation of particle size, work of cohesion and packing fraction distributions. The agglomerate strength of Ind decreased from 1.19 MPa for the binary Ind mixture to 0.84 MPa for 1DCP:20Ind mixture and to 0.42 MPa for 1DCP:2Ind mixture. Both extent of de-agglomeration, demonstrated by the concentration of the dispersed indomethacin distribution, and extent of dispersion, demonstrated by the particle size of the dispersed indomethacin, were in descending order of 1DCP:2Ind > 1DCP:20Ind > binary Ind. The addition of calcium sulphate dihydrate and talc also reduced the agglomerate strength and improved de-agglomeration and dispersion of indomethacin. While not definitively causal, the improved de-agglomeration and dispersion of a poorly water soluble drug by poorly water soluble components was related to the agglomerate strength of the cohesive matrix during dissolution.

1. Introduction

The dissolution rate of micronised, poorly water soluble drugs can be low, not only due to the low saturation solubility of the drug, but also because micronised drugs form agglomerates (McGinity et al., 1985) when their cohesive forces (for example, van der Waals forces) exceed detachment forces (for example, gravitational forces) (Visser, 1989). Agglomeration of particles decreases the surface area available for dissolution. Interactive mixtures of micronised drug and large carriers have been useful in the improvement of dissolution through reducing agglomeration by preferentially adhering the micronised cohesive particles onto larger carriers causing greater dispersion of these particles in the dissolution media (Nystrom and Westerberg, 1986). This can be especially useful at low drug concentration where there are surface and adsorption site available for the drug particles. If the drug concentration exceeds surface saturation, a portion of drug will exist in the formulation as agglomerates, often detached from the carriers (Alway et al., 1996; McGinity et al., 1985). These agglomerates have reduced surface area which will result in reduced dissolution of drug from concentrated drug-carrier formulations. The use of water soluble ternary components such as fine lactose has improved the dissolution of concentrated indomethacin-carrier formulations (Allahham and Stewart, 2007). This study showed that the formation of mixed agglomerates of ternary lactose with indomethacin particles, and rapid dissolution of the lactose in water during dissolution, increased the de-agglomeration and dispersion of the indomethacin particles. In another study, the dissolution of indomethacin in concentrated interactive mixtures was improved unexpectedly by the use of poorly water soluble inorganic salts (Tay et al., 2011a,b). However, it was not clear how the use of poorly water soluble inorganic salt improved dissolution although

Abbreviations: DCP, dibasic calcium phosphate dihydrate; CS, calcium sulphate dihydrate; SLS, sodium lauryl sulphate; AIC, Akaike Information Criterion; SEM, scanning electron microscope; PSD, particle size distribution; BET, Brunauer, Emmet and Teller.

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speculation was that the formation of weaker mixed agglomerates of indomethacin and poorly water soluble ternary components could be one of the mechanisms. Therefore, it still remains a matter of investigation as to whether poorly water soluble inorganic salts actually change the strength of these agglomerates and improve dissolution.

The lower de-agglomeration of dry powders inhaler formulations was found to be associated with the higher agglomerate strength of powders (Adi et al., 2006; Das et al., 2009). We have recently reported the direct estimation of the cohesive powder bed tensile strength or agglomerate strength (σ) from physical properties of the powder bed including particle diameter (d), packing fraction (ρ) (volume of particles/volume of aggregates) and work of adhesion or cohesion of particles (W) using Eq. (i) (Das et al., 2012; Kendall and Stainton, 2001):

$$\sigma = 15.6\left(\frac{\rho^4 W}{d}\right) \quad \text{(i)}$$

As cohesive powders are heterogeneous in nature having a distributions of particle size, work of cohesion and packing fraction, cohesive powders will have a distribution of agglomerate strength. In a recent study, the agglomerate strength of a cohesive powder for inhalation was estimated using numerical approaches and shown to be related to its propensity for de-agglomeration and aerosolisation (Das et al., 2012). Therefore, the current study relates agglomerate strength distributions of cohesive agglomerates of poorly water soluble drugs (indomethacin) and poorly water soluble inorganic salts (such as dibasic calcium phosphate dihydrate, calcium sulphate dihydrate and talc), present in the dissolution medium, to the dissolution of a poorly water soluble drug, indomethacin. In particular, the study was designed to test the following hypotheses: (a) that the addition of poorly water soluble ternary inorganic salts will reduce the agglomerate strength of cohesive agglomerates in the powder bed, and (b) that the extent of de-agglomeration and dispersion of the cohesive powders during in vitro dissolution will be related to the agglomerate strength of the cohesive agglomerates. The novelty of this study is that the relationship between agglomerate strength and de-agglomeration is explored to explain the counter-intuitive observation that poorly water soluble micronised excipients increase dissolution rate.

2. Materials and methods

2.1. Materials

Indomethacin (Sigma–Aldrich, St. Louis, MO, USA) was micronised and used as the model poorly water soluble drug. Three lactose carriers were used to prepare interactive mixtures: lactose monohydrate and lactose spray-dried (Lactose New Zealand, Hawera, NZ) and lactose-povidone granules prepared from lactose monohydrate and povidone (BASF, Ludwigshafen, Germany) (Tay et al., 2011a). Dibasic calcium phosphate dihydrate (DCP) (E. Mendell Co. Inc., Carmel, NY, USA), calcium sulphate dihydrate (CS) (Fluka, Buchs, Switzerland) and talc (Sigma–Aldrich Laborchemikalien GmbH, St Louise, MO, USA) were used as poorly water soluble agglomerate modifiers.

Milli-Q water (Millipore Milli-Q water purification system, Billerica, MA, USA), filtered and de-gassed through a 0.45 μm Durapore membrane (Millipore corporation, Carrigtwohill, County Cork, Ireland) by vacuum filtration, was used as the dissolution medium. Sodium lauryl sulphate (SLS) (0.005%, w/v) (Sigma, Castle Hill, NSW, Australia) was added to the dissolution medium to improve wettability of indomethacin in water (Kale et al., 2009).

2.2. Methods

2.2.1. Preparation of lactose-povidone carrier (Tay et al., 2011a)

Lactose monohydrate was wet granulated with 10% (w/w) aqueous povidone solution in a ratio of 9:1. The wet granules were oven dried at 50 °C for 24 h. In order to obtain the required size (106–250 μm), the dried granules were then comminuted using a mortar and pestle and classified.

2.2.2. Preparation of interactive mixtures

Both binary and ternary mixtures were prepared according to a validated method developed in our laboratory (Alway et al., 1996). In short, binary mixtures (5 g) were prepared by placing 20% (w/w) micronised indomethacin between equal amount of 80% (w/w) carriers in a glass jar. The jar was inverted several times and shaken by hand. At the end of each minute shaking, the jar was tapped to loosen any powder stuck to the jar wall or edges. For ternary mixtures, the ternary component (1% or 10%, w/w) was placed together with drug and mixed at the same way used for binary mixture.

2.2.3. Dissolution studies

Dissolution of indomethacin mixtures was conducted using an automated dissolution apparatus (Erweka, DT6, Heusenstamm, Germany) equipped with an online UV spectrophotometer containing six 10 mm UV-grade flow through cells (3021-Cecil UV spectrophotometer, Cecil Instruments Ltd., Cambridge, UK) and a multi-channel peristaltic pump (IPC 8 Ismatec pump; Ismatec SA, Switzerland). The USP Dissolution Apparatus 2 paddle method (United States Pharmacopeia 32/National Formulary 27, 2009) was used at a rotational speed of 100 rpm. A measured volume of 1000 ml Milli-Q water freshly filtered and degassed through a 0.45 μm Millipore membrane and equilibrated to 37.0 ± 0.5 °C was used as dissolution medium. The pH of the dissolution medium decreased as the dissolution of indomethacin progressed. This was published previously by our group (Tay et al., 2011a). Different weights of interactive mixtures (n = 4–6) were added to the dissolution apparatus to maintain an indomethacin concentration of 3 mg L^{-1} in each vessel in series (from vessel 1 to vessel 6 over 20 s in accordance with the sample loading time allowed in the dissolution software) to give sink conditions. Indomethacin concentrations were determined using the UV spectrophotometer at 2 min intervals over 120 min and dissolution data analysed using a Pharmatest dissolution software (V: 5.025-5b, Pharmatest, Hainburg, Germany).

2.2.4. Statistical modelling and analysis

Dissolution data were modelled using SigmaPlot 8.0 software (SPSS Inc., Point Richmond, CA, USA) which uses a Marquardt–Levenberg algorithm to find the coefficients (parameters) of the independent variables that give the best fit of the equation to the data (Marquardt, 1963). Using a mono-exponential (two parameters), bi-exponential (four parameters) or tri-exponential (six parameters) equation, the average of the undissolved concentrations (%) collected from all the vessels was tested against time. For estimating the initial concentrations and rate constants at different conditions, the curve fitting and parameter estimation using the specific exponential model was applied to individual data from each vessel.

These models were discriminated using the Akaike Information Criterion (AIC), the norm value and the F value. AIC is an almost unbiased estimator of the expected Kullback–Leibler information of a fitted model which is used to measure the difference between the actual and the fitted model (Allahham and Stewart, 2007). The norm value is the square root of the sums of squares when weighting is used and is an index of the closeness of fit. The F value indicates the contribution of the independent variables in predicting the