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Research paper

Drug agglomeration and dissolution – What is the influence of powder mixing?

Kamakshi Kale [a], Karen Hapgood [b], Peter Stewart [a,*]

[a] *Drug Delivery, Disposition and Dynamics, Institute of Pharmaceutical Science, Monash University, Vic., Australia*
[b] *Department of Chemical Engineering, Monash University, Vic., Australia*

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ABSTRACT

This study determined the influence of mixing speed and time on the dissolution and deagglomeration of a micronised, poorly water-soluble drug, indomethacin, in lactose interactive mixtures. Mixing occurred in a Turbula mixer; dissolution studies were performed using the USP paddle method, and the extent of deagglomeration was determined using modelling strategies and laser diffraction particle sizing of the powder mixtures. During low energy mixing at low rates and short mixing times, dissolution profiles showed an unusual flat asymptote indicating incomplete extents of dissolution caused by agglomerates that did not readily disperse in the dissolution medium. The study showed that increasing both speed and time of mixing increased the extent of dissolution and deagglomeration of the indomethacin powder. Nonlinear least squares modelling of the dissolution data using a sigmoidal equation provided estimates of the extent and rate of dissolution. Mixing speed and time had a much greater influence on the extent of dissolution which was controlled by deagglomeration than on the initial dissolution rate which was related to dispersed indomethacin. While some deagglomeration did occur at higher mixing energies, the deagglomeration of the indomethacin was not complete with only about 58–80% of indomethacin particles overlapping with the primary indomethacin particle size distribution. The significant outcome of this study was that mixing conditions have a major influence on the mixing quality, especially in areas where agglomerate characteristics influence performance.

1. Introduction

Poorly water-soluble drugs are often micronised to improve dissolution rates and bioavailability. When micronised drugs are mixed with excipients prior to processing into dosage forms, a complex array of particulate forms can exist due to cohesive and adhesive particle interactions occurring within the mixture. These particulate forms include interactive units and agglomerates of varying compositions [1]. Drug agglomeration is a major problem in controlling drug dissolution processes [2–5]; however, the impact of mixing conditions, mainly speed and time, on agglomeration is not completely understood and needs further investigation.

Mixing speed has been shown to influence the rate of mixing of cohesive powders, where the generation of stronger shear forces as a function of rotational speed produced improved mixing due to the cohesive inter-particulate forces of agglomerates being exceeded [6]. An investigation of the behaviour of agglomerates using a discrete element method found the pattern of deagglomeration to be affected by the frequency of shearing [7]. When subjected to steady shearing conditions, agglomerate break-up took place along one axis as opposed to oscillatory shearing, where fractured clusters reunited with the agglomerates. As expected, an increase in shear rate had a beneficial impact on dispersion of agglomerates. In another study, faster speeds and higher shear Turbula mixers were found to give rise to an enhanced, overall deagglomeration process [8]. A study using polymorphic forms of chloramphenicol palmitate found that mixing time impacted on the content variation of interactive mixtures, the quantity of unmixed drug powder within the mixtures and the drug attached to the walls of the mixing container [9]. The drug homogeneity was found to be a combination of random, non-interactive and interactive mixing processes. Longer mixing times caused greater adhesion between chloramphenicol palmitate and sugar beads. These outcomes were consistent with the findings of a study involving salicylic acid and erythrosine powder, which showed that longer mixing periods yielded reductions in non-adhered or free drug fraction that was stated to mix randomly [10]. A blending period of 3000 min was required to ensure the total deagglomeration of a number of poorly water-soluble compounds [11].

A study using sulphonamides discovered the same increasing trend in the adhesive tendency within interactive mixtures as a function of blending time [12]. This pattern was postulated to be a result of greater intermolecular interactions, fracture of large particles with longer times and the presence of agglomerates at short durations. An increased mixing time showed an unexpected, detri-

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* Corresponding author. Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), 381 Royal Parade, Vic. 3052, Australia. Tel.: +61 3 99039517; fax: +61 3 99039583.
E-mail address: peter.stewart@pharm.monash.edu.au (P. Stewart).

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mental effect on dissolution rates of micronised oxazepam and griseofulvin from interactive mixtures [13]. Longer mixing durations were suggested to result in delayed primary dissolution of a carrier due to a monolayer formation on its surface leading to subsequently slower drug particle dissolution. Duration of mixing was also one of the factors studied in an investigation, where thiacetazone interactive mixtures were prepared at durations ranging from 15 min to 5 h [14]. Mixing times greater than 15 min showed considerably greater dissolution of thiacetazone from interactive mixtures as opposed to that of the pure drug due to deagglomeration and redistribution of the drug on the carrier. Mixing duration also affected the volume diameter frequency distributions of the sparingly water-soluble drug, furosemide [15]. Although longer mixing durations showed reductions in the mean volume particle size, prevalence of agglomerates was also noted following a mixing duration of 64 min. Authors proposed that this behaviour was a result of agglomerates being concealed in the clefts and crevices located on the carrier surface and implied a lack of exposure of the agglomerates to shear forces during mixing.

Most of the literature studies have focussed on interactive mixtures, where the drug concentrations are relatively low and carrier surfaces are well below saturation. While the presence of agglomerates and rate of deagglomeration have limited the formation of truly interactive mixtures, the studies have not focussed on the mixtures where the content of micronised drug is greater, exceeding surface saturation, and where agglomeration of micronised drugs is likely to affect the quality of the mixtures. Therefore, this study will focus on the influence of mixing conditions on agglomeration of a cohesive, micronised drug, indomethacin in lactose interactive mixtures. The outcome of this research could then be used to further our understanding of agglomeration and design improved pharmaceutical powder formulations and processing techniques.

2. Materials and methods

2.1. Materials

The model drug, indomethacin (Sigma Chemical Company, USA), was micronised using a Laboratory Fluid Energy Mill (Model 75P; Chrispro Ltd., UK, compressed air 5.8 atm at 12.7 l s^{-1}). Lactose spray-dried for direct compression (Lactose New Zealand, New Zealand) was employed as the carrier material. Absolute alcohol (CSR, Australia) was used for the preparation of stock solutions for calibrations, homogeneity assessments and also for the particle size analysis of the un-fractionated spray-dried lactose. MilliQ water (Millipore Corporation, USA) was used in the preparation of buffer. The principal medium used for dissolution tests, particle size analysis and homogeneity assessments was phosphate buffer, pH 5 (British Pharmacopeia, 2005). Sodium lauryl sulphate, SLS (Sigma, USA), was used to prepare a 1.0% w/v solution, which was added to the dissolution medium to improve wettability of indomethacin.

2.2. Preparation of interactive mixtures

Mixing was performed in a Turbula mixer (T2F model; Willey A Bachofen AG, Maschinenfabrik, Basel, Switzerland). For all experiments, micronised indomethacin was placed between the two layers of spray-dried lactose in 30 g capacity clear glass jars before placing them into the mixer. All quantities used were accurately weighed using a Mettler balance (AT261 DeltaRange®, Mettler, Switzerland). The contents of the glass jars (20 g) were mixed at 23, 49 and 101 rpm. For each rotational speed, 1 g samples were removed from the mixer at time-points ranging from 2.5 to 20 min.

2.3. Homogeneity assessment

Homogeneity assessment was performed to test the efficiency of the mixing process. Eight binary indomethacin interactive mixtures were selected, and 20 samples of 50 ± 0.02 mg were randomly removed from each of the mixtures. Samples were then added to 50 ml of absolute ethanol in volumetric flasks and vigorously shaken prior to sonication for 20 min in a sonicator (Branson 5200). Aliquots removed from the sonicated solutions were added to 100 ml volumetric flasks with the volume being made up using phosphate buffer (pH 5.0). The final theoretical concentration of micronised indomethacin obtained in the buffer solution was 3 mg l^{-1}. Micronised indomethacin in each of the samples was then analysed via the validated UV spectrophotometric method. Averages (20 samples), standard deviations and percent CV (coefficient of variation) for each interactive mixture were calculated.

2.4. UV spectrophotometric assays

The concentration of indomethacin in the dissolution media was determined by an UV spectrophotometric assay using a Cecil CE 3021 spectrophotometer (Cecil Instruments Ltd., England). The wavelength of maximum absorbance of indomethacin for phosphate buffers of pH 6.0 was 267 nm. Samples were scanned from wavelengths of 200–400 nm to determine the wavelength of maximum absorbance. The absorbances of indomethacin in phosphate buffers at pH 5.0 using four concentrations from 2 to 8 mg l^{-1} (each with four replicates) were determined at 267 nm. Beer's law calibration plots of absorbance versus concentration showed no deviation from linearity with regression coefficients $\geqslant 0.9999$ and intercepts, which were not significantly different from zero ($p > 0.05$). The accuracy and precision of the assay over low, medium and high concentrations were 99.4–100.0% and 0.46–1.74%, respectively.

2.5. Dissolution studies

Dissolution tests were conducted using an Erweka, 6 flask automated apparatus (Erweka DT6, Germany) connected to a UV spectrophotometer (Cecil CE3021, Cecil Instruments Ltd., England) via an Isamtec® multi-channel pump. A USP/NF paddle method was used at a rotational speed of 100 rpm and at a temperature of 37.0 ± 0.5 °C. Dissolution medium (1000 ml) contained 995 ml of freshly de-gassed buffer solution or MilliQ water and 5 ml of 1% (w/v) SLS solution in order to improve indomethacin wettability. The buffer solution was de-gassed using an Air Admiral pump (Cole palmer; Extech equipment, Australia) and 0.45 μm Millipore filter (Millipore Corporation, USA).

Accurately weighed samples of interactive mixtures were subsequently added to each of the dissolution vessels using the count-down timer in the WinDis® program (dissolution software). Automatic sampling was performed, and absorbance readings (6 replicates) for indomethacin were recorded at the wavelength of maximum absorbance every 2 min over a period of 60 min.

2.6. Particle size analysis

A Malvern Mastersizer S (Malvern Instruments, UK) with a 300RF lens of path length 2.4 mm and a small volume dispersion unit (MS1) was employed for all particle size measurements. An adequate amount of material was added to approximately 50 ml of dispersion medium in the dispersion unit with a stirring speed set to a fixed mid-range. For each mixture, particle size distributions were recorded for five samples at an obscuration range of 10–30%. The particle size distributions of spray-dried and micronised lactose were determined using absolute ethanol as a disper-