

Investigation of Physical Changes in Drug-Carrier Interactive Mixtures on Blending

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Summary

An interactive mixture comprising a model drug, a surfactant and a carrier was created with the aim of investigating the state of drug agglomeration. A light-scatter method was developed to probe changes in agglomeration, by dissolving the excipients, leaving the drug in suspension. Over a period of days post-blending, the level of drug agglomeration appeared to increase. The dissolution rate of the drug was investigated, and this was found to decrease significantly on a similar timescale. This dissolution data was then modelled by considering that dissolution occurred from individually dispersed or aggregated particles, and the model supported an increase in agglomeration. Several hypotheses are proposed for the agglomerate increases, however the role of mechanical processing on fine particle agglomeration remains poorly understood, despite its key role in oral and inhaled drug delivery forms, and the desire to implement a "Quality by Design" ethos for risk management over the performance of these systems.

Background and Objectives

We have recently discussed some parallels in the behaviour of agglomerated fine particles in both oral and inhaled formulations (1, 2). In such formulations, the drug is often provided in a finely divided form in order to meet the delivery needs of the medication format. As an inhalation form, the particles are required to disperse into independent aerosol entities that are sufficiently small to avoid impaction on the route into the lungs. As oral forms, the particles are required to dissolve at an appropriate rate, to release the solvated material, which may have poor dissolution rate limitations. Consequently, oral delivery formulations may require micronised particles to improve dissolution rate. Inherent to finely divided drugs are the issues of adhesion and cohesion (autohesion), and these often lead to high levels of agglomeration (3). Agglomerate structure and the agglomerate mechanical strength which controls dispersion behaviour must be controlled if the product performance is to be achieved consistently. These issues are often addressed via the construction of interactive mixtures, to disperse the fine drug particles onto the surface of a larger excipient "carrier". The formation mechanisms of interactive mixtures are of considerable interest in this context (4).

In order to achieve an interactive mix structure, a degree of controlled mixing is inevitable, and this requires mechanical work on the powder (4). Much attention has recently focussed on the danger of mechanical activation during milling (5, 6), while little attention has considered issues of mixing (7). The objective of our work was to investigate the nature and extent of short-term dynamic changes to agglomerates within specific interactive mixtures following blending. A model micronised drug was formulated into a lactose-based interactive mixture containing a surface-active additive, following previously investigated systems (8, 9).

Materials, Methods and Results

Micronised nitrazepam (dv 6.9 μm) was used as the model adherent drug, sodium lauryl sulphate (sls) was also used as a micronised wetting aid, and a model carrier was prepared for the specific purpose of this study following a validated wet granulation method (10). Materials were conditioned prior to use. A previously validated method for preparing uniform interactive mixtures, without any detected comminution of carriers, was used (10) to produce the interactive mixture comprising 10% drug, 1% sls and 89% carrier. The powders were stored in sealed desiccators containing a layer of saturated salt solution to obtain storage conditions of approximately 33% \pm 3.0% humidity (RH). The desiccator was stored at 25.0 \pm 0.5°C.

An approach was developed, aimed at assessing the degree of “soft” drug agglomeration existing in the formulations. The approach was based on suspending powders in a liquid, designed to dissolve the carrier excipient, but leaving the drug particles, and then employing a laser diffraction particle sizing approach (Malvern Mastersizer S, Malvern Instruments, UK) to assess the degree of agglomeration. The purpose of this particle size analysis was to look for evidence of a change in apparent drug agglomerates over a period of hours to days after preparation. Powder samples were added to distilled water in the Small Volume Sample Dispersion Unit and the particles gently dispersed using a mechanical stirrer. Particle sizing was conducted under non-sink conditions. The particle size distribution was determined after 1 minute, at which stage the lactose carrier had dissolved, and so played no part in the size distributions with stable values recorded. The results for the systems are presented in Figure 1.

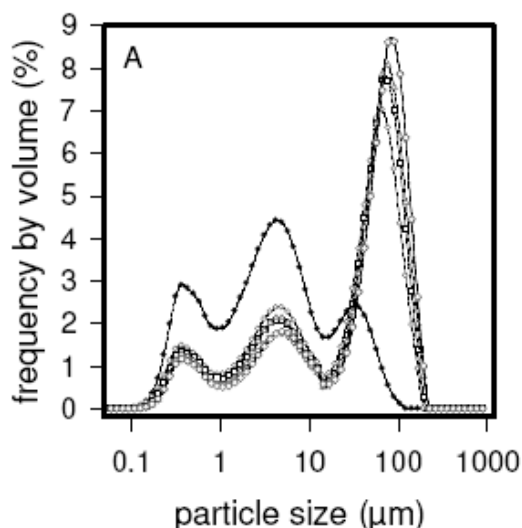


Figure 1: Particle size distribution of the nitrazepam interactive mixture at:

—●— time zero and after —○— 6, —□— 24, —△— 48, —▽— 96, and
—◇— 168 hours of storage.

Three modes were noted in each size distribution. The smallest, occurring at median size of approximately 0.2 μm , is suspected to be an artefact from non-optimising refractive index values, and so is recognized but not addressed as distinct from the dispersed primary drug particles here. The second at a median size of about 6 μm is considered to represent the majority of dispersed primary drug particles, and the third mode, between 20 and 100 μm , is proposed to represent the agglomerated drug entities.

This preliminary analysis suggested that the degree of drug “soft” agglomeration increased with storage time of these interactive mixtures.

In order to investigate and support this observation further, a previously used approach (11) was employed to try to correlate agglomeration level with dissolution behaviour over the same time period. Samples of interactive mixture were added to the dissolution apparatus in series and filtered samples were automatically assayed at 2 minute intervals over 60 minutes. The dissolution profiles of the 10% nitazepam, 1% sls and 89% carrier interactive mixture were determined at 0, 6, 24, 48, 96 and 168 hours after storage.

The dissolution rate was found to fall significantly over this timescale. These profiles are given in Figure 2

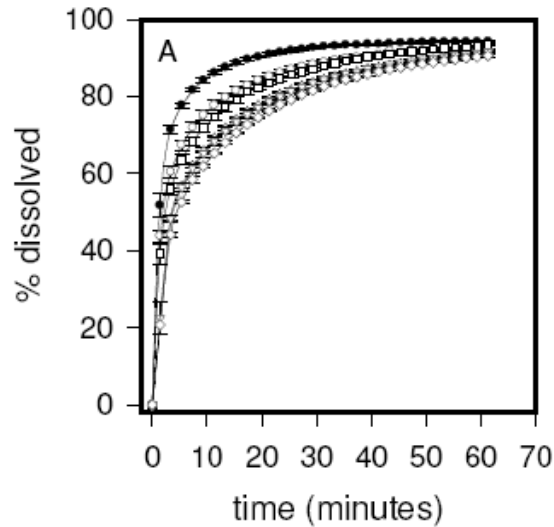


Figure 2. Dissolution profiles of 10% nitrazepam interactive mixtures at the following storage times:

● time zero and after ○ 6, □ 24, △ 48, ▽ 96
◇ and 168 hours of storage.

(Error bars represent standard error of mean {n = 6}).

The mixture indicated a steady progressive drop in nitrazepam dissolution rate over a one week period. Analysis of variance confirmed the changes were statistically significant ($p < 0.0001$) in the median percent dissolved after 6 hours storage and throughout all time periods up to one week.

This dissolution profile data was then modelled by considering that the nitrazepam dissolution occurred from distributions of individually dispersed or aggregated particles which existed after dissolution of the carrier after the interactive mixtures were placed in the dissolution medium (11). The data modelling demonstrated that the bi-exponential model of the form;

$$C = C_d \exp(-k_d t) + C_a \exp(-k_a t)$$

provided the best fit and the parameters of initial concentrations of dispersed particles and agglomerates and their respective rate constants were estimated.

Figure 3 represents the estimated initial concentration of dispersed particles and agglomerated particles for the interactive mixture. Increasing storage times led to an increase in agglomerate concentrations. From this model, the decrease in dissolution rate during storage was consistent with increase in agglomeration of the drug.

Discussion

This study shows apparent changes in the agglomeration state and dissolution profiles for an interactive mixture over a one week storage period following blending. Our modelling and particle sizing analysis suggests that these changes are due to relative changes in inter-particle adhesion, and consequent agglomerate composition and formation over the period of short-term storage.

Reports of changes to agglomerated drugs are not uncommon, following milling, but our finding suggests that such behaviour may be more broadly applicable. Indeed, anecdotal reports indicate that micronized pharmaceutical drugs, following incorporation into interactive mixtures for inhalation, may undergo drug agglomeration changes on subsequent storage, and care should be exercised in interpreting initial test data for these systems.

However, it is not clear what degree and form of charge, particle or material change is required to manifest these performance changes. Changes in adhesive forces during mechanical activation of powders are attributed to tribological electrostatic effects, non-electrical van der Waals contacts, from capillary based forces, and from formation of solid bridges. Given that moisture is implicated in many of these mechanisms, the effect of storage humidity will be the subject of a subsequent investigation (2). In addition, we shall investigate the role of the excipients, including sls and the carrier.

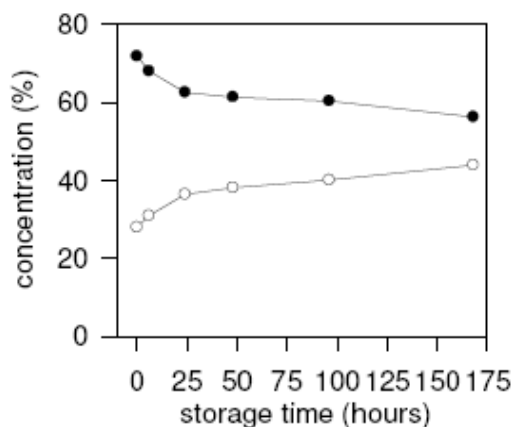


Figure 3. Estimated initial percent concentration of agglomerated and dispersed nitrazepam mixtures: Ca -○- and Cd -●-

Conclusions

We believe this is the first study to report such short-term agglomeration changes immediately following secondary processing. Several hypotheses are possible for the agglomerate increases, which relate to changes in electrostatic bipolar surface charge, to subtle rearrangement in particle orientations driven by van der Waals forces, to re-crystallisation at surfaces and to the role of moisture. The role of mechanical processing on fine particle agglomeration and agglomerate behaviour remains poorly understood, despite its key role in oral and inhaled drug delivery forms and beyond. The observations may have wider implications, both for interactive mixtures intended for inhalation, as well as for dissolution and for other powder-based drug delivery systems which include interactive mixtures with fine powders where agglomerate structure, and ultimately de-agglomeration play an important role in functionality. This study emphasizes the need for enhanced understanding if we are to implement a "Quality by Design" ethos to improve long term control and risk management over the performance and physical stability of these systems.

References

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