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Stages in spheronisation: Evolution of pellet size and shape during spheronisation of microcrystalline cellulose-based paste extrudates

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ABSTRACT

The stages of extrudate breakup and rounding to form spheroidal pellets were investigated for MCC/water pastes and some MCC/water/calcium carbonate pastes using the interrupted technique reported by Lau et al. (2014). A new quantitative parameter, named 'dumb-bellity', was developed to monitor the formation and disappearance of 'dumb-bell' shaped pellets in the early stages of the rounding process. Tests using mixtures of coloured extrudates confirmed that attachment of small fragments ('fines') to the waist of pellets was not responsible for the transition from dumb-bell to more spheroidal shapes. The results confirmed the findings of Lau et al., that rounding was the rate-limiting step. Extrudates prepared with up to 20 wt.% calcium carbonate, (the carbonate representing a hard, active pharmaceutical ingredient), were subject to the same spheronisation mechanism. The time to spheronise the carbonate-containing pastes was longer, which could be related to the increased deformation resistance of these materials.

1. Introduction

Extrusion–spheronisation (E–S) is used in the pharmaceutical sector for manufacturing pellets with high sphericity and density [8]. E–S is a two-stage process in which the particulate solids are firstly combined with a liquid (the binder) into a paste that is extruded through dies or screens to give cylindrical extrudates, and the extrudates are then spheronised on a rotating friction plate to give pellets [18,19]. The term pellet is used here to differentiate the assembly from the constituent particles.

Conine and Hadley [7] proposed that the basic criterion for a successful spheronisation is that the extrudate must be able to break up into sections that are plastic enough to be rounded by the frictional forces on the rotating plate and collisions with pellets and walls. The collisions can also cause attrition, generating fines, which can attach to larger pellets (termed 'mass transfer' by [9]). Developing formulations for E–S is complicated, as the paste material must also be malleable enough to be extruded and for the pellets to be rounded. It must also be strong enough for the extrudates and the pellets to retain their shape, and break without creating many fines.

The evolution of pellet size and shape during spheronisation is a complex process and the current level of understanding is mainly at the stage of identifying phenomena, whereas the physics of other granulation methods such as those that employ high shear are well enough understood to allow predictive numerical simulation (e.g. [5]). The three phenomenological models for spheronisation in the literature are summarised in Fig. 1.

Model A: [14]

The cylindrical extrudates break into short lengths which collide with each other, the friction plate and the walls. The rods undergo plastic deformation which causes them to become rounded cylinders: these are further rounded to a dumb-bell, then to an ellipsoid or egg-shape and finally a sphere.

Model B: [1]

In addition to breakage, the rods are rounded by collisions with the walls and other pellets and become twisted, eventually breaking into sub-pellets with rounded and fractured sides. The latter faces are folded together by the rotating and frictional forces on the friction plate to form a near-spherical pellet. This folding action was claimed to explain why some pellets contain a cavity.

Model C: [12]

The pellets pass through the dumb-bell stage and become more round by attachment of fines in the mid-plane or 'waist' region of the pellet. Koester et al. [9] also advocated this model, in which attrition generates fines which subsequently re-attach to larger pellets.

All three models emphasise the role played by collisions between pellets and between pellets and the spheroniser surfaces. The fines

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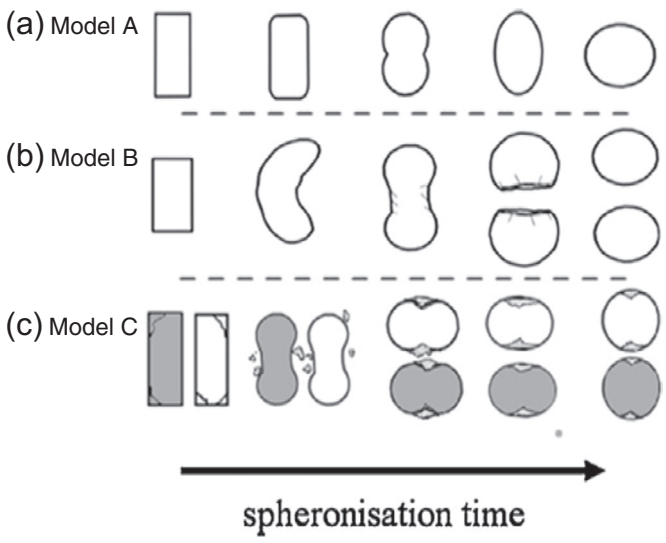

Fig. 1. Spheronisation mechanisms according to (*a*) Rowe [14]; (*b*) Baert et al. [1]; (*c*) combined deformation and agglomeration mechanism [9,12].

play a major part in Model C, and this model may be specific to formulations which tend to form fines.

Knowledge of the phenomenology is important as this can guide the simulations of pellet breakage and plastic deformation (such as those reported by [16]) in constructing quantitative physical models. By comparison, measurement of the distribution of instantaneous pellet positions and velocities is better understood, as a result of development of measurement techniques (e.g. [2]).

There have been few detailed studies of spheronisation mechanisms to date. This paper employs the approach taken by Lau et al. [11] to investigate the spheronisation of a simple microcrystalline cellulose (MCC)/water paste. The E–S formulations of water-tolerant active pharmaceutical ingredients (APIs) regularly incorporate MCC as an excipient, as this 'gold standard' material [10] provides the paste with good water retention properties and ductility. A similar 45 wt.% MCC/water paste was studied: this material has been shown to undergo E–S readily [21].

Lau et al. [11] performed spheronisation tests starting with the same number (20) of identical extrudates, stopping tests after different times in order to measure the number of pellets, their size and shape. With this relatively small number of extrudates, collisions were dominated by wall-pellet events. They found little evidence to support Model B (twisting). Fig. 2 summarises the stages that they observed, showing two pathways determined by how the extrudate breaks. When an extrudate broke to give a short rod (length ≤ roughly two extrudate diameters) the rod rounded off, presumably as a result of plastic deformation. Longer rods tended to go through a dumb-bell stage and eventually pass through an approximately elliptical stage en route to a final spheroidal shape. This paper extends the Lau et al. study by investigating whether dumb-bell shaped pellets collect fines at their waist (Model C) and to monitor the evolution of dumb-bell shape more explicitly. A simple quantitative measure of dumb-bell shape, termed 'dumb-bellity', was created for the latter purpose. This concavity metric is evaluated by an analysis of images of individual pellets, which is performed by numerical algorithms in Matlab®. The reliability of this measure, and its sensitivity to imaging and experimental artefacts, is explored. The influence of the initial amount of extrudate loaded into the spheroniser was also investigated.

Application of the results to pharmaceutical formulations is demonstrated by a short investigation of spheronisation of extrudates prepared with calcium carbonate particles in the MCC/water paste. The carbonate is insoluble in water and represents a 'hard' active

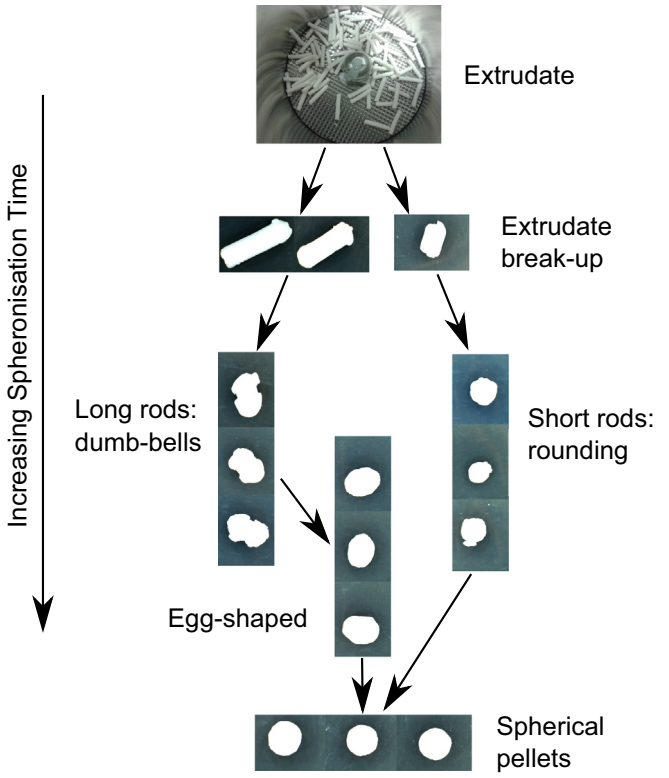

Fig. 2. Phenomenological model for spheronisation of MCC paste extrudates (reproduced from [11]).

pharmaceutical ingredient (API). Zhang et al. [21] studied the E–S behaviour of similar formulations, and these new data provide further insight into their results.

2. Materials and methods

2.1. Extrudate preparation

Microcrystalline cellulose (Avicel PH101, FMC Corporation, Ireland) was provided by MSD Devlab (Hoddesdon, UK). The MCC powder characteristics were reported previously by [20]: moisture content ~3 wt.%; particle shapes, measured by Malvern Morphologi G3 automated microscope, ranging from small irregular cuboids to larger fibrous rods, with sizes ranging from 2 to 260 μm and Sauter mean diameter of 49.1 μm.

45 wt.% MCC/water pastes were prepared following the procedure reported by [20]. Dry MCC powder and deionised water were mixed together using a planetary mixer fitted with a 'K'-beater attachment and a lid to minimise evaporation (Kenwood Chef KM200, Kenwood Ltd, UK). The mixer had seven speed settings, labelled S1-7, the lowest four of which were used, S1 being the lowest: water was added over 1 min while stirring at S1 and the mass then subjected to a speed/time mixing sequence of S1, 2 min; S2, 3 min; S3, 3 min; S4, 2 min. Material adhering to the bowl was scraped back into the mass with a spatula in between mixing steps. The paste was stored in a sealed plastic sample bag at room temperature for 4 h before extrusion.

A subset of tests was performed with a grey version of the paste to see whether material transferred between extrudates. Bryan et al. [4] had demonstrated this 'solid staining' approach to monitor the formation of static zones in MCC paste extrusion. The paste was prepared by replacing 1% of the MCC powder mass with graphite powder (BDH, size distribution in terms of circle equivalent diameter, d_{CE}, volume