

## Non-aqueous formulations for ram and screen extrusion-spheronisation

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### **Abstract**

The use of non-aqueous cellulose-based formulations for extrusion-spheronisation (E-S) is investigated. A 10 wt% hydroxypropyl cellulose/isopropyl alcohol solution (HPC/IPA) was identified as a suitable sticky liquid binder for preparing non-aqueous pastes. Preliminary tests were performed on a series of pastes using a ram as well as a laboratory roller screen extruder, since the former is commonly used in batch testing and the latter replicates the shear range in a manufacturing screen extruder. Pellets with acceptable size and shape distributions were obtained with Avicel<sup>®</sup> HFE-102 NF/HPC/IPA for ram E-S, and with Avicel<sup>®</sup> RC-591/HPC/IPA for screen E-S. Further investigation was performed with calcium carbonate added as a model active pharmaceutical ingredient. Both formulations were able to generate pellets with acceptable size and shape characteristics at up to 50 wt% carbonate loading: further work is required to optimise yields.

**Keywords:** non-aqueous formulations, extrusion, spheronisation, pellets

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## 1. Introduction

Extrusion-spheronisation (E-S) is a granulation method which yields dense pellets of high sphericity and with narrow size distribution. A particulate paste is extruded through dies or screens to generate strands which break into shorter lengths and are formed into spherical granules by contact with a rotating friction plate (Vervaet et al. 1995; Newton, 2008; Wilson and Rough, 2007; Dhandapni *et al.*, 2012). The material needs to exhibit plastic behaviour, enabling extrusion, as well as suitable fracture toughness to facilitate breakage and ductility to allow rounding (Mascia *et al.*, 2010). Limited adhesion is also needed to avoid pellets sticking or overmassing.

For many pharmaceutical products these properties have been achieved using formulations based on micro-crystalline cellulose (MCC) and its derivatives, with water as the liquid phase. MCC and its derivatives absorb water to provide a soft solid mass which can be combined with significant volume fractions of solid active pharmaceutical ingredients (APIs) to give composite materials which are suitable for E-S processing. A number of studies have used MCC/water pastes as the matrix to investigate the influence of drug loadings and water content on E-S processing parameters and pellet quality (e.g. Tomer *et al.*, 2001; 2002). Furthermore, pellets with high API loading have been generated using aqueous MCC formulations (Podczek and Knight, 2006; Di Pretoro *et al.*, 2010).

APIs which are incompatible with water require non-aqueous liquid binders. Moisture-free formulations are particularly important for herbal drugs such as garlic powder, as they can be usually highly hygroscopic and the moisture promotes degradation (Bley *et al.*, 2009). One approach is to use a different granulation method such as hot melt granulation, where the API is combined with a polymer to generate pellets (Bialleck and Rien, 2011; Palem *et al.*, 2015; Leelakanok *et al.*, 2018; Tun *et al.*, 2018). Another is to combine a particulate excipient with a 'sticky' non-aqueous binder to give a cohesive mass which is suitable for extrusion and spheronisation. This differs from the soft solid approach as the excipient particles do not soften to the same extent. Chatlapalli and Rohera (1998) were able to obtain acceptable pellets in terms of size and shape, friability, *etc.* using a hydroxypropyl cellulose (HPC)/isopropyl alcohol (IPA) solution with different types of cellulose.

Relatively few studies of E-S with non-aqueous binders have been reported and those employing non-aqueous solvents with cellulose are summarised in Table 1. Mascia *et al.* (2010) demonstrated that dimethyl sulfoxide (DMSO) could be used in E-S formulations with MCC as its similar polarity to water allowed it to interact with MCC in a similar manner. However, DMSO is currently not permitted for use in solid oral dosage forms (SODFs), so alternative approaches are required.

This paper reports an investigation of two routes for preparation of non-aqueous cellulose-based formulations, *i.e.* that of a soft solid (where the solid phase becomes plastic on addition of a simple organic solvent) and one based on solid particles with a sticky liquid binder (such as an organic solvent containing dissolved polymer). A schematic of the two routes is shown in Figure 1. For the former route, preliminary tests were conducted with MCC-based pastes prepared with the FDA-approved non-aqueous solvents in Table 2: these tests established that none were suitable for E-S. For the latter route, both ram and screen extrusion tests were performed on sticky binder paste formulations. Ram extrusion testing employed a small laboratory ram extruder, representing a typical configuration used to test formulations, and screen extrusion was performed using a laboratory roller screen device (LRS) (Mascia, 2008), which subjected the paste to a strain profile closer to that experienced in commercial manufacturing-scale screen extruders. Negative results as well as positive outcomes are reported for completeness sake and since they are expected to assist other workers investigating this topic. One potential sticky binder formulation was identified using each extrusion device and their potential was investigated further in a short study involving different loadings of an inert model API, namely calcium carbonate.

## 2. Materials and Methods

### 2.1 Materials

#### 2.1.1 Solids

Eight cellulose-based powders were investigated as excipients for non-aqueous formulations: Avicel<sup>®</sup> MCC (PH101), two grades of hydroxypropyl methylcellulose (HPMC E6P and K4M), two grades of hydroxyethyl cellulose (HEC 250HX and 250M), Avicel<sup>®</sup> HFE-102 NF (co-processed MCC and mannitol), Avicel<sup>®</sup> CE-15 (= co-processed MCC and guar gum) and Avicel<sup>®</sup> RC-591 (co-processed MCC and sodium carboxymethylcellulose). Table 3 summarises the powder characteristics, including dry particle size and shape distribution data obtained using a Morphologi G3 automated microscopy system (Malvern Instruments Ltd, Worcestershire, UK). Particle shape was quantified using the aspect ratio,  $AR$ , and circle equivalent diameter,  $d_{CE}$  (*i.e.* the diameter of a circle having the same area as that of the 2-D image of the particle).

Calcium carbonate (calcite) powder obtained from Pumex UK Ltd (Newcastle-under-Lyme, Staffordshire, UK) was used as a model API. Particle sizing was performed on a Coulter LS230 laser diffraction device using deionised water as dispersant. The Sauter ( $D[3, 2]$ ) and mean ( $\pm$  standard deviation) diameters were found to be 1.3 and 8.0 ( $\pm$  6.9)  $\mu\text{m}$ , respectively. The difference in these parameters indicate that the particle sizes are not monodispersed.

#### 2.1.2 Solvents

The solvents used, including one ester (ethyl acetate), one ketone (acetone) and four alcohols (methanol, ethanol, butyl alcohol and isopropyl alcohol (IPA)), were of laboratory reagent grade (purity > 99.5 %) and were obtained from Fisher Scientific UK Limited (Loughborough, UK). All are registered in the Food and Drug Administration (FDA) inactive ingredient database for pharmaceutical solid oral dosage forms (SODFs).

### 2.2 Methods

#### 2.2.1 Paste preparation

*Preparation of MCC/organic solvent pastes (hand mixing)*

These scoping tests required a small amount of non-aqueous paste (*i.e.* 20 g). The MCC

powder was measured out into a glass bowl and solvent slowly added until the solid surface was wet and there was a small amount of excess liquid. A spatula was used for mixing and distributing the liquid evenly through the solids. Preparation was conducted at constant temperature and humidity ( $22 \pm 1^\circ\text{C}$  and  $32 \pm 2\%$ , respectively). A sample of 45 wt% MCC/water paste was prepared in the same manner. These pastes were dried and observations are summarised in Table 2.

*Preparation of sticky-liquid binder pastes (mechanical mixing)*

Following the work of Chatlapalli and Rohera (1998) featuring MCC, HPMC (E6P) and HEC (250HX) powders as excipients, pastes were prepared with a binder containing 10 wt% HPC in solution with IPA. Screening tests on HPC/IPA solutions with HPC mass concentrations between 3 and 10 wt% indicated that the 10 wt% HPC/IPA solution was most promising. The IPA charge was heated to  $50^\circ\text{C}$  and weighed again, and more IPA added if any had been lost to evaporation during heating. The HPC powder was added and mixed using a magnetic stirrer rotating at 700 rpm for 30 to 40 min at a temperature of around  $40^\circ\text{C}$ . This gave a transparent liquid.

The rheology of the binder was studied under steady and oscillatory shear on a Bohlin CVO 120 rheometer under controlled shear rate mode. Tests employed 25 mm diameter, sandpaper-roughened parallel plates with a 1 mm gap. Samples were loaded on the bottom plate and exposed to pre-shear at 0.5 Pa for 10 s followed by 10 s rest before testing. In shear rate sweeps, the strain rate was ramped up from  $0.1\text{ s}^{-1}$  to  $100\text{ s}^{-1}$  and back to  $0.1\text{ s}^{-1}$ , with a minimum delay time of 5 s. This range of shear rates bracketed the values expected in the screen extruders, e.g. an apparent shear rate at hole land of laboratory screen extruder is  $4.1\text{ s}^{-1}$  (Zhang *et al.*, 2013b). Oscillatory tests employed a stress amplitude sweep, from 0.1 to 1000 Pa, at a constant frequency of 1 Hz. Tests were performed at  $20^\circ\text{C}$  (room and extrusion temperature) and  $30^\circ\text{C}$  (mixing temperature). A cup enclosure minimised evaporation. Each test was performed at least twice to check reproducibility.

The steady shear results in Figure 2(a) show that the binder was viscous and thixotropic. At  $20^\circ\text{C}$  the binder exhibited shear-thinning power law behaviour above  $0.3\text{ s}^{-1}$ , corresponding to a shear stress of approximately 25 Pa. Figure 2(b) shows that the

binder was linearly viscoelastic at lower stresses ( $< 0.5$  Pa) . Both the elastic and viscous moduli,  $G'$  and  $G''$ , respectively, were almost constant, with  $G''$ , slightly larger than  $G'$ , until approximately 20 Pa (as indicated by  $\tau_{20}$  and  $\tau_{30}$  in Figure 2(b) for 20 and 30 °C, respectively) above which  $G'$  decreased noticeably. These results indicate that the binder behaved as a gel at low shear rates (Mezger, 2006).

The pastes in Table 4 were initially prepared with a mass ratio of excipient to HPC/IPA solution of 2.5, except for HPMC(E6P) where extra HPC/IPA binder was added because the paste with a mass ratio of 2.5 appeared dry compared to the other mixtures. The powder and binder were loaded into a planetary mixer with a 'K'-beater attachment (Chef KM200, Kenwood Ltd, UK) and stirred at minimum speed for 2 min. Any caked paste was then dislodged from the wall of the bowl by a plastic spatula. Mixing was continued for another minute, during which time additional IPA was added to generate an extrudable wet mass (judged by eye). The wet mass was then stirred for 1 min at each speed setting of 1, 2 and 3, pausing to dislodge any caked paste from the side of the bowl between steps. For speed settings 1 and 3, the maximum shear strain rate that the paste experienced was estimated to be of the order  $100 \text{ s}^{-1}$  and  $250 \text{ s}^{-1}$ , respectively (see Bryan *et al.*, 2015). The paste was stored in a sealed plastic bag at room temperature for 1 hour before extrusion to allow the material to equilibrate (Zhang *et al.*, 2011).

Pastes containing calcite as pseudo-API were prepared as above but with the calcite and excipient powders dry mixed at minimum speed for 1 minute before the addition of binder. The protocol for mixing of solids and liquid was the same as above.

### 2.2.2 Extrusion-spheronisation (E-S)

Ram extrusion experiments were performed using a 50 kN strain frame (Zwick/Roell, Zwick Testing Machines Limited, Leominster, UK) configured to operate as a ram extruder (see Mascia and Wilson, 2008): the set-up is commonly used for lab testing. Preliminary tests used a smaller ram and barrel (ram diameter,  $D_{\text{ram}}$ , 11.0 mm; barrel internal diameter,  $D_{\text{barrel}}$ , 11.1 mm,  $L_{\text{barrel}} = 77.7$  mm) to reduce the amount of material required for tests. The square entry dies consisted of either a single, coaxial

hole of diameter  $D = 2$  mm and length,  $L = 4$  mm, or a regular array of 7 holes with  $D = 2$  mm and  $L = 8$  mm representative of a multi-holed die plate or screen (see Zhang *et al.*, 2011). All parts were constructed from stainless steel apart from the polythene ram seal. The ram was moved along the barrel at a set speed and the force imposed on the ram measured using a load cell. Tests were performed at different ram velocities. The force was used to calculate the extrusion pressure,  $P_{ex}$ , from  $P_{ex} = 4 \times \text{extrusion force} / \pi(\text{ram diameter})^2$ .

Larger amounts of paste were extruded using a standard ram and barrel ( $D_{ram} = 24.8$  mm,  $D_0 = 25.0$  mm, filled to a height of approximately 125 mm) with a multi-holed die (33 holes,  $D = 1$  mm,  $L = 2$  mm, see Zhang *et al.*, 2011), which provided a closer match to the hole fraction of the laboratory roller screen extruder (LRS). The ram velocity ( $V_{ram}$ ) was set at  $2.5 \text{ mm s}^{-1}$ , corresponding to a die land velocity ( $V_{die}$ ) of  $0.047 \text{ m s}^{-1}$ .

The LRS, described in detail by Zhang *et al.* (2013a,b), was used here to simulate the industrial screen extruder geometry. The cylindrical roller is fitted with blades, which push paste towards the nip between the roller and the screen. The paste is compacted at the nip region and is subjected to high stress, prompting the material to flow through screen holes. The diameter ( $D_s$ ) and length ( $L_s$ ) of the holes in the screen are both 1 mm. Each of the formulations in Table 4 was tested on the LRS with blade height 0.5 mm, nip gap 0.3 mm, and roller speed of 8 rpm.

After extrusion, about 30 g of extrudates were spheronised using a Caleva Spheronizer 120 (Caleva Process Solutions Ltd, Dorset, UK), fitted with a 120 mm diameter stainless steel cross-hatched friction plate. The yield of pellets was calculated from

$$Y = \frac{\text{mass of spheronisation products prior to drying (g)}}{\text{mass of extrudates loaded into the spheroniser (g)}} \quad (1)$$

Pastes or pellets were dried in air in a fan oven at  $60 \text{ }^\circ\text{C}$  until a constant mass was obtained, and the sample total IPA content was determined by mass loss on drying.

The dried sample was then sorted using four sieves with mesh cut-off sizes of 3350, 2000, 425 and 355  $\mu\text{m}$ . Pellets in the size range 425 – 2000  $\mu\text{m}$  were analysed further using a digital video image analysis system (Canty Sizer, JM Canty Ltd, Dublin).



### 3. Results and discussion

#### 3.1 Ram extrusion

Small-scale ram extrusion tests ( $D_{\text{sram}} = 11.00$  mm) using pastes A, G and H (see Table 4 for formulations) showed dramatic increases in extrusion force, as shown in Figure 3, with  $P_{\text{ex}}$  exceeding 30 MPa, resulting in the test being terminated. No extrudate was produced and sticky liquid was found in the tooling when the equipment was dismantled. These observations indicate that acute liquid phase migration (LPM) had occurred, caused by the binder filtering through the solids matrix in response to the compaction pressure. In the presence of water, however, these powders gave extrudable pastes as a result of the water being absorbed by the biopolymer and thereby softening the particle matrix.

In comparison, relatively steady values of  $P_{\text{ex}}$  were observed for pastes B, D, E and F. Figure 3(c) shows that the HEC(250HX) and HEC(250M) materials (*i.e.*, pastes D and E) gave quite even extrusion profiles, but in both cases the extrudates were brittle and were broken during transport or gentle handling: the extrudates were hence expected to break into fines upon spheronisation. The HPMC(E6P) and Avicel<sup>®</sup> HFE-102 NF extrudates (from paste B and F, respectively) were relatively stiff and retained their shape during transport, so these were considered further. Small ram extrusion was not performed on paste C, as similar behaviour to paste B was expected.

Both HPMC-based pastes and the Avicel<sup>®</sup> HFE-102 NF-based pastes were investigated further. It was noticed that Avicel<sup>®</sup> HFE-102 NF-based pastes were quite sensitive to the binder composition, so a series of Avicel<sup>®</sup> HFE-102 NF pastes, prepared with HPC/IPA solution and some excess IPA, were studied (Table 5). The ratio of Avicel<sup>®</sup> HFE-102 NF solid to binder solution was kept approximately constant at 2.5 kg/kg and the total IPA content was varied in order to generate good pellets. Figure 4 shows that pastes B, C and F3 gave steady extrusion profiles with the standard barrel ( $D_0 = 25.0$  mm).

The two excipient types differed in spheronisation outcomes (30 g extrudates spheronised at 600 rpm for 90 s). Although the HPMC-based pastes (*i.e.*, pastes B and C) could be extruded, the extrudates did not perform well during spheronisation. The spheronisation yields of the B and C paste extrudates were about 88.3 and 84.1 wt%,

respectively. The pellet sizing results in Table 6 indicate that both the HPMC-based pastes gave broad size distributions with a coefficient of variation (COV, defined as standard deviation/mean) of  $\sim 50\%$ . Some dumb-bells were evident with both pastes, and both the size and shape distributions of the pellets lay outside the acceptable range for pharmaceutical products.

Avicel<sup>®</sup> HFE-102 NF-based pastes proved to give superior extrusion performance: all the pastes gave steady extrusion pressure profiles (similar to Figure 4(b)). The reasons for this superior performance are not currently known, but the smooth surface and non-folded edges of these particles are known to give good flow properties in the dry state (Desai, *et al.*, 2012; Daraghmeh, *et al.*, 2010) and this is likely to carry over into the paste regime.

In addition, spheronisation of the Avicel<sup>®</sup> HFE-102 NF pastes could be performed at 600 rpm for 90 s. The additional IPA content effectively controlled the spheronisation behaviour: lower IPA contents gave extrudates which did not round into pellets, whilst high IPA contents promoted agglomeration and overmassing. The mean  $d_{CE}$  and aspect ratio of the 425-2000  $\mu\text{m}$  size fractions are given in Table 5.

Paste F3 gave the best pellet product at 600 rpm in terms of a mean aspect ratio close to 0.8 and a relatively small coefficient of variation for  $d_{CE}$  and  $AR$ . The pellet quality of paste F3 could be improved by spheronising at 1600 rpm for 2 min. The yield obtained at the latter conditions was about 94.2 wt%, with more than 96 wt% of the pellets in the range 425 – 2000  $\mu\text{m}$ . The size and shape distributions for this paste (measured by Canty Sizer) are presented in Figure 5. The number distribution is bimodal, with modal  $d_{CE}/D$  values of 0.65 and 1.25. Most pellets lie in the size range of 0.55 to 1.55 mm and have aspect ratios above 0.80. The pellet mean  $d_{CE}$  and aspect ratio are  $1.00 \pm 0.33$  mm and  $0.90 \pm 0.07$ , respectively.

In comparison, Zhang *et al.* (2013b) presented results for a ram E-S of a 45 wt% MCC/water paste under similar conditions as this study. They reported spheronisation yields around 96%, but with some large agglomerates (unacceptable for capsule filling and tableting). These results show that Avicel<sup>®</sup> HFE-102 NF/HPC/IPA paste (paste F3)

can produce pellets with acceptable characteristics, albeit after some process optimisation.

## 3.2 Screen extrusion using the LRS

### 3.2.1 Primary extrusion trials

The pastes in Table 4 were also tested using the LRS. In most cases, extrusion was stopped when enough extrudates (*i.e.* about 30 g) were obtained for spheronisation. LRS performance is summarised in Table 7. Most extrudates were short, brittle and exhibited surface fractures, except for the extrudates from paste H, Avicel<sup>®</sup> RC-591/HPC/IPA, which were relatively long with smooth surfaces.

About 30 g of extrudates were spheronised at 600 rpm for 90 s. The dried pellets were sieved and the results are summarised in Table 7. The mass percentages of the pellets in the range of 425 – 2000  $\mu\text{m}$  are plotted against the spheronisation yield in Figure 6, where the overall E-S yield can be seen to differ between formulations. Dried pellets in the size range of 425 – 2000  $\mu\text{m}$  were analysed using the Canty Sizer. The mean  $d_{\text{CE}}$ , aspect ratios and associated coefficient of variations are presented in Table 7.

Figure 6 shows that pastes F and H (*i.e.*, Avicel<sup>®</sup> HFE-102 NF/HPC/IPA and Avicel<sup>®</sup> RC-591/HPC/IPA, respectively) gave a relatively high overall yield, along with an acceptable pellet mean diameter and aspect ratio (reported in Table 7). According to pharmaceutical industry standards, the COV of the pellet  $d_{\text{CE}}$  and aspect ratio is expected to be smaller than 20% (Seiler and Ward, 2012). Table 7 indicates that the COV of the  $d_{\text{CE}}$  values all lay above 20%. Future work should focus on reducing this value.

The pellets from paste F (Avicel<sup>®</sup> HFE-102 NF) were brittle and some of them broke on handling during the collection and analysis operations (notably vibration during sieving and sizing). In comparison, the Avicel<sup>®</sup> RC-591 pellets from paste H were less friable, although dumb-bells were observed in the sample. It is noteworthy that neither of these pastes extruded satisfactorily in ram extrusion (See Figure 3): the LRS generates lower extrusion pressures and did not appear to compact the material to the point which promoted liquid phase migration observed above. The reason why the

Avicel<sup>®</sup> RC-591 performs well is not clear: this material is known to form a gel when wetted by water (Zhao *et al.*, 2011) and further work is required to determine whether this occurs with the alcohol. Based on the observations, paste H (based on Avicel<sup>®</sup> RC-591) was selected as a potential E-S formulation for further testing.

The observations of differences in friability highlight that this property needs to be considered before a formulation can be considered for manufacture. Friability was not considered in detail in these studies as the focus is on the ability to generate pellets, *i.e.* suitability for extrusion and spheronisation. Friability is a factor that can be applied after a route to generate pellets is identified.

### 3.2.2 Further tests on paste H (Avicel<sup>®</sup> RC-591/HPC/IPA)

As reported above, dumb-bells were generated from spheronisation of paste H LRS extrudates at 600 rpm for 90 s. Alternatively, the results shown in Section 3.1 imply that an increase in the spheronisation speed to 1600 rpm could change the products from cylindrical extrudate segments into pellets (see Figure 5). Screen extrusion of paste H was therefore followed by spheronisation at 1600 rpm. Spheronisation was paused every minute to monitor progress. Visually acceptable pellets (in terms of their size and shape) were observed and spheronisation was stopped after 3 minutes. The spheronisation yield was about 37.1 wt%, which was considered to be very low. The remaining product existed as fines, which collected under the spheroniser plate. The fines were not subjected to further analysis.

The pellets were then dried and sieved. About 89 wt% of pellets lay in the size range of 425 – 2000  $\mu\text{m}$ , and the size and shape distributions are presented in Figure 7. The mean  $d_{\text{CE}}$  and aspect ratio were  $0.79 \pm 0.20$  and  $0.84 \pm 0.09$ , respectively. The pellet size distribution is unimodal with modal  $d_{\text{CE}}/D = 0.65$ . Most of the pellets in the size range of 0.35 – 1.05 mm were of acceptable shape quality as their aspect ratios are  $\geq 0.8$ . The standard deviation of the mean aspect ratio is relatively small, which implies narrow size and shape distributions.

These results are now compared with those reported by Zhang *et al.* (2013b) for a 45 wt% MCC/water paste using similar LRS E-S conditions. They obtained a mean  $d_{\text{CE}}$  of 1.13

$\pm 0.32$  mm and a mean aspect ratio of  $0.85 \pm 0.09$ . The non-aqueous paste, H, gave a similar mean aspect ratio, smaller mean  $d_{CE}$ , smaller COV for shape, and noticeably lower spheronisation yield (37.1% vs 98.8%). The latter value would need to be improved significantly for manufacturing applications: the other results suggest that screen E-S of paste H could produce acceptable pellets. Optimising the experimental conditions to increase the yield represents a topic for future work.

### **3.3 Investigation of E-S of the non-aqueous candidate formulations with CaCO<sub>3</sub>**

Calcium carbonate was chosen as a model API and it was added to the potential formulations (*i.e.* paste F3, Table 6 and paste H, Table 4). The CaCO<sub>3</sub> loading in each formulation was set at 50 wt% of the total dry ingredients. Notional formulations are given in Table 8. Ram extrusion and spheronisation were performed on the CaCO<sub>3</sub>/Avicel<sup>®</sup> HFE-102 NF/HPC/IPA paste (labelled API1). LRS E-S was performed on the CaCO<sub>3</sub>/Avicel<sup>®</sup> RC-591/HPC/IPA paste (labelled API2). The extrusion conditions were those described previously. Relatively long extrudates were obtained with both pastes. About 30 g of the extrudates were spheronised at 1600 rpm for 2 min.

Photographs of the dried pellets are shown in Figure 8. The pellet size and shape distribution plots from Canty Sizer analysis are given in Figure 9 and the distribution parameters from sieving are in Table 8.

Compared to the paste F3 (see Section 3.1), the spheronisation yield of paste API1 is lower (53.1 wt% vs 94.2 wt%), which is likely due to API1 containing less liquid and being less cohesive. During spheronisation, extrudate attrition generated many fines. The spheronisation yield of the API2 paste was similarly much lower than that of paste H (17.8 wt% vs 37.1 wt%) (see Section 3.2). Optimising the liquid content of the formulations is recommended for future work in order to improve the spheronisation yield.

The pellet sieving results, presented in Table 8, show that most of the dry pellets (more than 85 wt%) lay in the 425 – 2000  $\mu\text{m}$  size range. Figure 9 shows that both pellet size distribution curves are unimodal, with modal  $d_{CE}/D$  values of 0.65 and 0.75 mm for the API1 and API2 pellets, respectively. The mean  $d_{CE}$  of both pellets is about 0.80 mm,

although the standard deviation of the API1 pellets is slightly larger. Figure 9 also shows that about 99% of the API1 pellets lie in the size range of 0.45 to 1.45 mm and have an aspect ratio  $> 0.8$ . About 97% of the API2 pellets between 0.35 – 1.05 mm had aspect ratios above the threshold value, indicating that they are of acceptable shape.

The results for these high API loaded pellets are comparable to those reported by Zhang *et al.* (2013b) for 50 wt% CaCO<sub>3</sub>/MCC/water paste under similar processing conditions. Ram E-S gave a mean  $d_{CE}$  of  $1.57 \pm 0.31$  mm and an aspect ratio of  $0.87 \pm 0.09$ . LRS E-S of 50 wt% CaCO<sub>3</sub>/MCC/water paste gave a mean  $d_{CE}$  of  $0.85 \pm 0.23$  mm and aspect ratio of  $0.86 \pm 0.09$ , which are similar to paste API2.

### 3.4 Application considerations

The results obtained with simple organic solvents as binder liquids (the ‘soft solids’ approach) confirm the findings of Mascia *et al.* (2010), that translation of MCC performance with aqueous binders into the non-aqueous formulation space is not currently feasible with FDA-approved solvents. The inclusion of a dissolved polymer in the non-aqueous solvent (the ‘sticky binder’ approach) is required to give pastes (or doughs) suitable for extrusion-spheronisation. This will also require careful selection of the solvent and soluble polymer, which is likely to introduce API-specific considerations. It is also necessary to consider alternative solid excipients to simple microcrystalline cellulose, or blends, to optimize the pellet properties.

Two formulations based on a sticky binder were identified as potential candidates for extrusion spheronisation by the two extrusion routes. Their performance is compared in Table 9, with and without CaCO<sub>3</sub> addition, alongside that of a reference aqueous-MCC formulation. The reduction in yield when CaCO<sub>3</sub> is added is significant, indicating that the formulation may need tailoring to the API by, for example, adjusting the quantity of solvent added.

It is significant that the most promising candidate for ram extrusion-spheronisation differed from that for screen extrusion-spheronisation. Ram extrusion is popular in laboratory development as it allows small amounts of material to be tested, and this result indicates that further optimization would be required as part of scale up.

#### 4. Conclusions and Outlook

Two types of water-free formulations for the production of pharmaceutical pellets via paste extrusion-spheronisation were investigated, shown schematically in Figure 1: ones in which liquid was absorbed by the excipient to give a soft solid, and ones incorporating a sticky liquid binder to provide cohesion

##### *'Soft solid'*

The work on the soft solid route considered one excipient, MCC (PH101), known to perform well with water, and focused on investigating mixtures of the MCC with FDA-registered SODF solvents. These proved to be unpromising: the mixtures appeared brittle and became powdery after drying, indicating that MCC did not retain the solvent and that there was little irreversible interaction between the solid and liquid phases. In addition, ram extrusion promoted severe LPM and the pastes became too dry (stiff) to be extruded. These observations agree with the findings of Mascia *et al.* (2010) who reported that only solvents with high polarity (*e.g.* water and DMSO) caused MCC fibres to swell and form a mechanically stable structure to retain liquid under pressure. The MCC/organic solvent mixtures were thus considered as unsuitable formulations for producing pharmaceutical pellets via E-S.

It is not unexpected that non-aqueous solvents proved unsuitable for softening MCC, as the mechanism of softening relies on charge interactions with the biopolymer. One could now ask whether other approved excipients (whether natural or synthetic polymers) can be converted to a deformable state by contact with a non-aqueous solvent, where absorption is driven by a different mechanism. This route is not available to crystalline excipients such as calcium carbonate (calcite). The question could also be phrased as to whether the material's glass transition temperature can be modified accordingly by contact with solvent. The softening temperature of fats and waxes can be adjusted by altering their composition, a feature which is exploited in the food sector, and there is scope for using similar materials in pharmaceutical formulations as long as reliable sources were available. One attraction of adopting excipients from the food sector is the existence of safety-related information related to ingestion *etc.*

##### *'Sticky binder'*

The sticky binder approach employed one binder liquid, a viscoelastic 10 wt% HPC/IPA

solution, which was mixed with different cellulose-based excipients. Avicel® HFE-102 NF/HPC/IPA and Avicel® RC-591/ HPC/IPA pastes were identified as potential non-aqueous formulations for ram and screen extrusion, respectively. Although the Avicel® HFE-102 NF/HPC/IPA paste was less cohesive than the Avicel® RC-591/HPC/IPA paste, the former was highly compacted in ram extrusion, giving dense and stiff extrudates which could be formed into good pellets. In tests with a model API loading of 50 wt%, using CaCO<sub>3</sub>, both non-aqueous formulations generated pellets of acceptable quality. The spheronisation yield was low in both cases. Optimising formulation liquid content and processing conditions is needed to improve the yield, for which the Design of Experiments approach is well suited. This stage would need to include considerations of product performance such as friability.

With the sticky binder approach, the solid matrix retains its shape as a result of the liquid wetting the particles and the combination of binder elasticity and viscosity retarding the deformation of the mass when shear is applied. The cohesive strength could be expected to increase when the elasticity of the binder phase is increased (*e.g.* Ferstl *et al.*, 2019), as long as the mass can be extruded. Similar solid-wetting binders could be used with other excipients.

A variation on this approach would be to employ a non-aqueous viscoplastic fluid as a binder, where the yield strength of the fluid gives rise to cohesion in the composite. There are many examples of viscoplastic fluids with water in the continuous phase, including dense suspensions, clays, emulsions and foams. Several modelling clays feature non-aqueous formulations. The challenge with these materials is achieving good mixing in preparing the wet mass. Ultimately one would want to be able to control the onset of plastic behaviour, and one method, exploited in melt-spheronisation, is by adjusting temperature. Here, a temperature sensitive binder such as a lipid is added warm so that it can be mixed and the material extruded, then spheronised at a lower temperature which promotes setting and plastic behavior during spheronisation. The patent of Young *et al.* (2002) features a variation of this technique.

An alternative method for introducing cohesive behavior in suspensions is by adding a small amount of a second immiscible liquid phase to form capillary suspensions (Koos, 2014). Possible combinations include alcohols (and alcohol-polymer blends) and oils,



as long as the API is compatible with both. This represents an area for future work.

### **Open Data Statement**

A link to the data associated with this paper, held at the University of Cambridge Data Repository, will be provided here if the paper is accepted for publication.

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## ***Nomenclature***

### ***Roman***

|               |   |             |
|---------------|---|-------------|
| $AR$          | Aspect ratio  | -           |
| $d_{CE}$      | Circle equivalent diameter                          | m           |
| $D$           | Die hole diameter                                   | m           |
| $D_{ram}$     | Standard ram diameter                               | m           |
| $D_s$         | Screen hole diameter                                | m           |
| $D_{sbarrel}$ | Small barrel diameter                               | m           |
| $D_{sram}$    | Small ram diameter                                  | m           |
| $D_0$         | Standard barrel diameter                            | m           |
| $D[3,2]$      | Sauter mean diameter (volume-surface mean diameter) | m           |
| $G'$          | Elastic modulus                                     | Pa          |
| $G''$         | Viscous modulus                                     | Pa          |
| $L$           | Die length  | m           |
| $L_s$         | Screen hole length                                  | m           |
| $L_{sbarrel}$ | Length of small barrel                              | m           |
| $P_{ex}$      | Extrusion pressure                                  | Pa          |
| $V_{die}$     | Die land velocity in ram extrusion                  | $m\ s^{-1}$ |
| $V_{ram}$     | Ram velocity  | $m\ s^{-1}$ |
| $Y$           | Spheronisation yield                                | %           |

### ***Greek***

|             |                          |    |
|-------------|--------------------------|----|
| $\tau_{20}$ | Critical stress at 20 °C | Pa |
| $\tau_{30}$ | Critical stress at 30 °C | Pa |

## **Acronyms**

|      |                                  |
|------|----------------------------------|
| API  | Active pharmaceutical ingredient |
| COV  | Coefficient of variation         |
| DMSO | Dimethylsulfoxide                |
| E-S  | Extrusion-spheronisation         |
| HEC  | Hydroxyethyl cellulose           |
| HPC  | Hydroxypropyl cellulose          |
| IPA  | Isopropyl alcohol                |
| LPM  | Liquid phase migration           |
| LRS  | Laboratory roller screen         |
| MCC  | Microcrystalline cellulose       |
| SODF | Solid oral dosage form           |

Table 1 Reported studies of E-S of non-aqueous formulations (after Mascia *et al.*, 2010).

| Wet massing liquid               | Solid excipient                           | Pellet quality   | Source                          |
|----------------------------------|---|--|---------------------------------|
| ethanol                          | MCC                                       | Crumbled on handling   | Millili <i>et al.</i> (1990)    |
| IPA                              | MCC                                       | Crumbled on handling   | Schröder and Kleinebudde (1995) |
| HPC <sup>(1)</sup> in IPA (q.s.) | MCC, HPMC <sup>1</sup> , HEC <sup>2</sup> | Pellets of acceptable hardness, friability, density and sphericity | Chatlapalli and Rohera (1998)   |
| DMSO                             | MCC                                       | Pellets of acceptable shape and mechanical strength                | Mascia <i>et al.</i> (2010)     |
| Propylene glycol                 | MCC                                       | Acceptable yield, sphericity and friability                        | Gurram <i>et al.</i> (2016)     |

(1) HPMC - hydroxypropyl methylcellulose; (2) HEC - hydroxyethyl cellulose

*Table 2 Investigation of MCC-based paste drying behaviour after granulation with DMSO and FDA-registered-SODFs solvents at 20 °C (after Anslyn and Dougherty (2006) and Reid et al. (1986), ranked in order of dielectric constant) of the solvent. Each paste was dried in air at 60 °C until a constant mass was obtained.*

| Liquid              | Dielectric constant, $\psi^{(1)}$ | MCC-based pastes                             |                               |  |
|---------------------|-----------------------------------|--|-------------------------------|--|
|                     |                                   | Notional liquid content <sup>(2)</sup> (wt%) | Measured liquid content (wt%) | Drying behaviour   |
| water               | 78                                | 55.0   | 56.2                          | MCC/water agglomerates retained their shape when handled gently; dried material remained in the shape of agglomerates.   |
| DMSO <sup>(3)</sup> | 47                                | –  | –                             | Not investigated in this study, as it is not an FDA-approved non-aqueous solvent for use in solid dosage forms; see Mascia <i>et al.</i> (2010)  |
| methanol            | 33                                | 61.3   | 58.9                          | Wet agglomerates fell apart on handling; after drying, the MCC returned to its original powdery-state.   |
| ethanol             | 25                                | –  | –                             | Not investigated in this study, as Mascia <i>et al.</i> (2010) reported that ethanol-based paste could not be ram extruded due to significant liquid phase migration; see Mascia <i>et al.</i> |
| acetone             | 21                                | 61.5   | 47.1                          | Significant amount of acetone evaporation during mixing (as seen from the difference between notional and measured liquid content); MCC/acetone paste became powdery after drying              |
| isopropyl alcohol   | 20                                | 49.2   | 48.1                          | Similar to that of MCC/methanol combination  |
| butyl alcohol       | 12                                | 50.0   | 50.8                          | Negligible liquid evaporation during mixing; after drying, the mixture returned to its original powdery-state  |
| ethyl acetate       | 6                                 | 61.5   | 59.0                          | Similar to that of MCC/methanol combination  |

Keys: (1) Mathematically,  $\psi$  is the ratio of the permittivity of the medium to that of vacuum. This dimensionless parameter is often called the relative permittivity.

(2) The notional liquid content was calculated according to the amount of solid and liquid that was initially mixed.

(3) Not FDA registered SODF solvent.



Table 3 Characteristics of the cellulose powder excipients

| Category                   | Excipient   | Manufacturer                   | Bulk density <sup>1</sup><br>(kg m <sup>-3</sup> ) | Powder<br>moisture<br>content <sup>2</sup> (wt%) | Particle size and shape distribution parameters ( $\pm$ S.D.) |                                |                             |                 |
|----------------------------|---|--------------------------------|--|--|---|--------------------------------|-----------------------------|-----------------|
|                            |   |                                |  |  | Maximum $d_{CE}$<br>( $\mu$ m)                                | Minimum $d_{CE}$<br>( $\mu$ m) | Mean $d_{CE}$<br>( $\mu$ m) | AR<br>(-)       |
| microcrystalline cellulose | MCC (PH101)   | FMC BioPolymer <sup>3</sup>    | 200 - 500  | 3.0  | 217.0   | 0.52                           | 25.6 $\pm$ 25.1             | 0.63 $\pm$ 0.19 |
| cellulose ether            | HPMC (E6P)  | Ashland Inc. <sup>4</sup>      | X  | 1.8  | 156.5   | 0.52                           | 16.1 $\pm$ 23.1             | 0.65 $\pm$ 0.16 |
|                            | HPMC (K4M)  | Ashland Inc. <sup>4</sup>      | X  | 1.7  | 268.3   | 0.52                           | 15.0 $\pm$ 22.5             | 0.66 $\pm$ 0.17 |
|                            | HEC (250HX)   | Ashland Inc. <sup>4</sup>      | X  | 3.2  | 254.4   | 0.52                           | 22.7 $\pm$ 30.1             | 0.68 $\pm$ 0.17 |
|                            | HEC (250M)  | Hercules <sup>5</sup>          | X  | 3.7  | 444.0   | 0.52                           | 14.2 $\pm$ 27.3             | 0.69 $\pm$ 0.17 |
|                            | co-processed<br>excipients – cellulose<br>with other polymers | Avicel <sup>®</sup> HFE-102 NF | FMC BioPolymer <sup>3</sup>                        | 200 - 500  | 2.7   | 317.9                          | 0.52                        | 12.3 $\pm$ 20.9 |
|                            | Avicel <sup>®</sup> CE-15                                     | FMC BioPolymer <sup>3</sup>    | 400  | 3.2  | 151.1   | 0.52                           | 12.9 $\pm$ 11.1             | 0.71 $\pm$ 0.15 |
|                            | Avicel <sup>®</sup> RC-591<br>stabilizer                      | FMC BioPolymer <sup>3</sup>    | 600  | 3.3  | 149.8   | 0.52                           | 12.1 $\pm$ 12.2             | 0.77 $\pm$ 0.14 |

Keys: 1. From manufacturer's data sheet.

2. The moisture content was determined by drying about 10 g of powder at a temperature of 60 °C under 200 mbar vacuum until a constant mass was obtained.

3. FMC BioPolymer, 1735 Market Street, Philadelphia, PA 19103.

4. Ashland Inc. 50 E. RiverCenter Blvd. P.O. Box 391 Covington, KY 41012-0391 USA.

5. Hercules Doel B.V.B.A Aqualon division, Geslecht 2, B-9130 Doel (Beveren), Belgium.

X. Information not provided in the manufacturer's data sheet.

Table 4 Formulations studied in the first set of non-aqueous formulations. Binder: 10 wt% HPC in IPA.

| Paste | Excipient          | Nominal content (wt%) |        |           |                         | Measured IPA content (wt%) |       |                |
|-------|--------------------|-----------------------|--------|-----------|-------------------------|----------------------------|-------|----------------|
|       |                    | excipient             | binder | extra IPA | total IPA in the paste‡ | binder                     | paste | pellets (LRS†) |
| A     | MCC (PH101)        | 49.7                  | 19.9   | 30.4      | 48.4                    | 88.6                       | 42.7  | 39.0           |
| B     | HPMC (E6P)         | 41.6                  | 22.4   | 36.0      | 56.0                    | 88.6                       | –     | 41.2           |
| C     | HPMC (K4M)         | 49.7                  | 19.8   | 30.5      | 56.1                    | 88.1                       | 50.8  | 43.8           |
| D     | HEC (250HX)        | 56.6                  | 22.7   | 20.7      | 41.2                    | 89.5                       | 36.7  | 31.8           |
| E     | HEC (250M)         | 58.9                  | 23.8   | 17.3      | 38.8                    | 90.4                       | 34.1  | 26.8           |
| F     | Avicel® HFE-102 NF | 49.5                  | 20.2   | 30.3      | 48.5                    | 89.7                       | 42.7  | 40.6           |
| G     | Avicel® CE-15      | 59.6                  | 24.1   | 16.3      | 38.0                    | 89.1                       | 30.7  | 19.2           |
| H     | Avicel® RC-591     | 66.0                  | 26.3   | 7.7       | 31.4                    | 89.1                       | 27.9  | 22.5           |

‡ This is the sum of the IPA in the binder and the extra IPA

† No pellets were obtained from these tests, as the pastes were extruded using the small ram configuration.

Table 5 Composition and pellet characteristics of the initial Avicel<sup>®</sup> HFE-102 NF/HPC/IPA pastes following ram extrusion and spheronisation at 600 rpm for 90 s. The associated yields are reported in Table 9.

| Paste | Notional paste IPA content (wt%) | Measured IPA content (wt%) |               | Cantyl Sizer<br>(number distribution basis, 425-2000 $\mu\text{m}$ fraction) |                 | COV, $d_{CE}$<br>(%) | COV, AR<br>(%) |
|-------|----------------------------------|----------------------------|---------------|--|-----------------|----------------------|----------------|
|       |                                  | paste                      | pellets (ram) | mean $d_{CE}$ (mm)   | mean AR (-)     |                      |                |
| F1    | 42.9                             | 37.3                       | 35.2          | 1.12 $\pm$ 0.31  | 0.75 $\pm$ 0.14 | 28                   | 19             |
| F2    | 40.2                             | 38.4                       | 35.2          | 1.17 $\pm$ 0.32  | 0.75 $\pm$ 0.14 | 27                   | 19             |
| F3    | 42.4                             | 39.3                       | 37.9          | 1.40 $\pm$ 0.41  | 0.77 $\pm$ 0.13 | 29                   | 17             |
| F4    | 43.7                             | 41.0                       | 39.9          | 1.45 $\pm$ 0.63  | 0.79 $\pm$ 0.12 | 43                   | 15             |
| F     | 48.5                             | 43.4                       | 42.8          | 2.40 $\pm$ 1.79  | 0.83 $\pm$ 0.10 | 75                   | 12             |

Table 6 Size and shape analysis for pellets generated from HPMC/HPC/IPA (ram) extrudates spheronised at 600 rpm for 90 s. The shaded column indicates the pellets that were characterised using the Canty Sizer.

| Paste | Excipients | Sieving (wt%) |              |               | Canty Sizer<br>for 425 –2000 µm sample<br>(number distribution basis) |                          | COV of $d_{CE}$ (%) | COV of aspect ratio (%) |
|-------|------------|---------------|--------------|---------------|---|--------------------------|---------------------|-------------------------|
|       |            | < 355 µm      | 355 – 425 µm | 425 – 2000 µm | mean $d_{CE}$<br>(mm)   | mean aspect ratio<br>(-) |                     |                         |
| B     | HPMC(E6P)  | 4.4           | 0.8          | 94.8          | 1.14 ± 0.53   | 0.77 ± 0.13              | 46                  | 17                      |
| C     | HPMC(K4M)  | 15.6          | 2.6          | 81.9          | 0.81 ± 0.41   | 0.83 ± 0.11              | 50                  | 13                      |

Table 7 Paste LRS performance and pellet sieving results. Shaded column indicates the pellets that were characterised using the Canty Sizer. 30 g of extrudates were spheronised at 600 rpm for 90 s.

| Paste | Solid excipients   | Extrudates  | Sieving (wt%)          |                               |                             |                              |                                 | Canty Sizer analysis<br>(Number distribution basis) |                 | COV, $d_{CE}$<br>(%) | COV, AR<br>(%) |
|-------|--------------------|---|------------------------|-------------------------------|-----------------------------|------------------------------|---------------------------------|---|-----------------|----------------------|----------------|
|       |                    |   | < 355<br>$\mu\text{m}$ | 355<br>– 425<br>$\mu\text{m}$ | 425 – 2000<br>$\mu\text{m}$ | 2000 –<br>3350 $\mu\text{m}$ | $\geq$<br>3350<br>$\mu\text{m}$ | mean $d_{CE}$<br>(mm)                               | mean AR<br>(-)  |                      |                |
| A     | MCC (PH101)        | Short & brittle extrudates with surface fractures   | 24.6                   | 14.6                          | 60.8                        | 0                            | 0                               | 0.66 $\pm$ 0.21                                     | 0.86 $\pm$ 0.09 | 32                   | 10             |
| B     | HPMC (E6P)         | Similar to above  | 61.2                   | 7.4                           | 29.2                        | 2.2                          | 0                               | 0.74 $\pm$ 0.23                                     | 0.82 $\pm$ 0.10 | 31                   | 12             |
| C     | HPMC (K4M)         | Similar to above  | 52.6                   | 4.8                           | 42.6                        | 0                            | 0                               | 0.77 $\pm$ 0.28                                     | 0.84 $\pm$ 0.09 | 36                   | 11             |
| D     | HEC (250HX)        | Similar to above  | 17.3                   | 4.8                           | 71.6                        | 2.8                          | 3.5                             | 0.83 $\pm$ 0.38                                     | 0.81 $\pm$ 0.11 | 46                   | 14             |
| E     | HEC (250M)         | Similar to above  | 15.3                   | 9.9                           | 71.8                        | 0.2                          | 2.7                             | 0.73 $\pm$ 0.31                                     | 0.81 $\pm$ 0.10 | 42                   | 12             |
| F     | Avicel® HFE-102 NF | Similar to above  | 1.4                    | 1.1                           | 92.1                        | 3.8                          | 1.6                             | 0.83 $\pm$ 0.44                                     | 0.84 $\pm$ 0.10 | 53                   | 12             |
| G     | Avicel® CE-15      | Significant hole blockage, small amount of extrudates obtained after a prolonged running time | 24.2                   | 7.0                           | 68.8                        | 0                            | 0                               | 0.55 $\pm$ 0.27                                     | 0.84 $\pm$ 0.10 | 49                   | 12             |
| H     | Avicel® RC-591     | relatively long extrudates with smooth surfaces   | 0.4                    | 0.2                           | 81.0                        | 10.7                         | 7.6                             | 1.13 $\pm$ 0.33                                     | 0.80 $\pm$ 0.10 | 29                   | 13             |

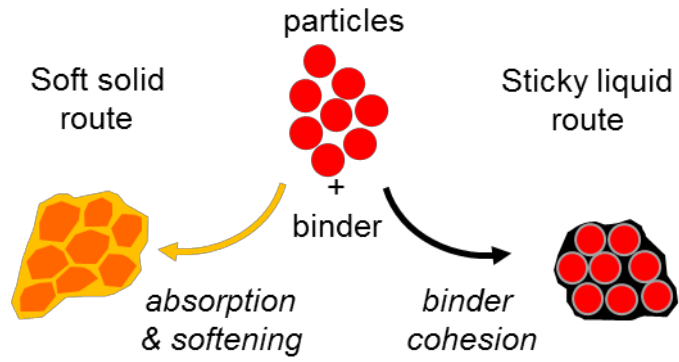
*Table 8 Size distributions of API1 and API2 pellets obtained by sieving and Canty Sizer analysis.*

| Paste  | API1                                 |   | API2 |   |
|--|--------------------------------------|---|------|---|
|  |                                      | CaCO <sub>3</sub> /Avicel <sup>®</sup> HFE-102 NF/HPC/IPA |      | CaCO <sub>3</sub> /Avicel <sup>®</sup> RC-591/HPC/IPA |
|  | CaCO <sub>3</sub>                    | 29.8  |      | 39.8  |
| Nominal content (wt%)                            | excipient                            | 29.8<br>(Avicel <sup>®</sup> HFE-102 NF)                  |      | 39.8<br>(Avicel <sup>®</sup> RC-591)                  |
|  | binder                               | 11.9  |      | 15.8  |
|  | extra IPA                            | 28.6  |      | 4.6   |
| Extrusion  |                                      | Ram   |      | LRS   |
| Spheronisation yield (wt%)                       |                                      | 53.1  |      | 17.8  |
| Sieving (wt%)                                    | < 355 μm                             | 9.3   |      | 2.1   |
|  | 355 – 425 μm                         | 5.2   |      | 2.4   |
|  | 425 – 2000 μm                        | 85.5  |      | 92.1  |
|  | 2000 – 3350 μm                       | 0   |      | 0   |
|  | ≥ 3350 μm                            | 0   |      | 3.1   |
| Canty Sizer analysis (number distribution basis) | mean $d_{CE}$ (mm)                   | 0.79 ± 0.23   |      | 0.80 ± 0.15   |
|  | 425 – 2000 μm fraction mean $AR$ (-) | 0.88 ± 0.08   |      | 0.84 ± 0.09   |

Table 9 Summary of pellet parameters for non-aqueous formulations. Die land and screen hole diameters were both 1 mm. Data reported by Zhang et al. (2013b) for MCC/water pastes are included for comparison.

|   | Ram extrusion                 |  |   |                                    | LRS extrusion            |  |   |                                    |                  |
|---|-------------------------------|--|---|------------------------------------|--------------------------|--|---|------------------------------------|------------------|
|   | Avicel® HFE-102 NF (paste F3) | 45 wt% MCC/water paste (Zhang et al., 2013b) | CaCO <sub>3</sub> /Avicel® HFE-102 NF/binder/IPA paste (API1) | CaCO <sub>3</sub> /MCC/water paste | Avicel® RC-591 (paste H) | 45 wt% MCC/water paste (Zhang et al., 2013b) | Avicel® RC-591 /binder/IPA paste (API2) | CaCO <sub>3</sub> /MCC/water paste |                  |
| Spheronisation yield (wt%)                    | 94.2                          | 96   | 53.1  | 97.6                               | 37.1                     | 98.8   | 17.8                                    | 96.3                               |                  |
| Dry pellets in 425 – 2000 µm size range (wt%) | 96.4                          | –  | 85.5  | > 92                               | 88.6                     | > 91   | 92.1                                    | 100                                |                  |
| Size range (mm)                               | 0.3 – 2.2                     |  | 0.3 – 1.6   | 0.8 – 2.8                          | 0.3 – 2.0                | 0.25 – 2.45                                  | 0.4 – 1.6                               | 0.4 – 1.8                          |                  |
| Mode of $d_{CE}/D$ (-)                        | 0.65 & 1.25                   | Large agglomerates                           | 0.65  | ~1.2                               | 0.65                     | 1.0  | 0.75                                    | 0.75                               |                  |
| Canty Sizer analysis                          | Aspect ratio > 0.8 (number %) | 0.25 – 1.55 mm (98.9 %)                      | (unacceptable for capsule filling and tableting)              | 0.45 – 1.45 mm (99.4 %)            | 0.8 – 2.0 mm (93 %)      | 0.35 – 1.05 mm (91.5 %)                      | 0.55 – 1.25 mm (-)                      | 0.35 – .05 mm (96.7 %)             | 0.4 – 1.2 mm (-) |
| Mean $d_{CE}$ (mm)                            | 1.00 ± 0.33                   |  | 0.79 ± 0.23   | 1.57 ± 0.31                        | 0.79 ± 0.20              | 1.13 ± 0.32                                  | 0.80 ± 0.15                             | 0.85 ± 0.23                        |                  |
| Mean aspect ratio (-)                         | 0.90 ± 0.07                   |  | 0.88 ± 0.08   | 0.87 ± 0.09                        | 0.84 ± 0.09              | 0.85 ± 0.09                                  | 0.84 ± 0.09                             | 0.86 ± 0.09                        |                  |

Key: – Not reported.



*Figure 1 Schematic of approaches used in non-aqueous formulations. (left) The yellow binder is absorbed by the red particles to give softer, yellow particles. (right) The black binder interacts with the solid phase and may change the surface but not the bulk solid.*



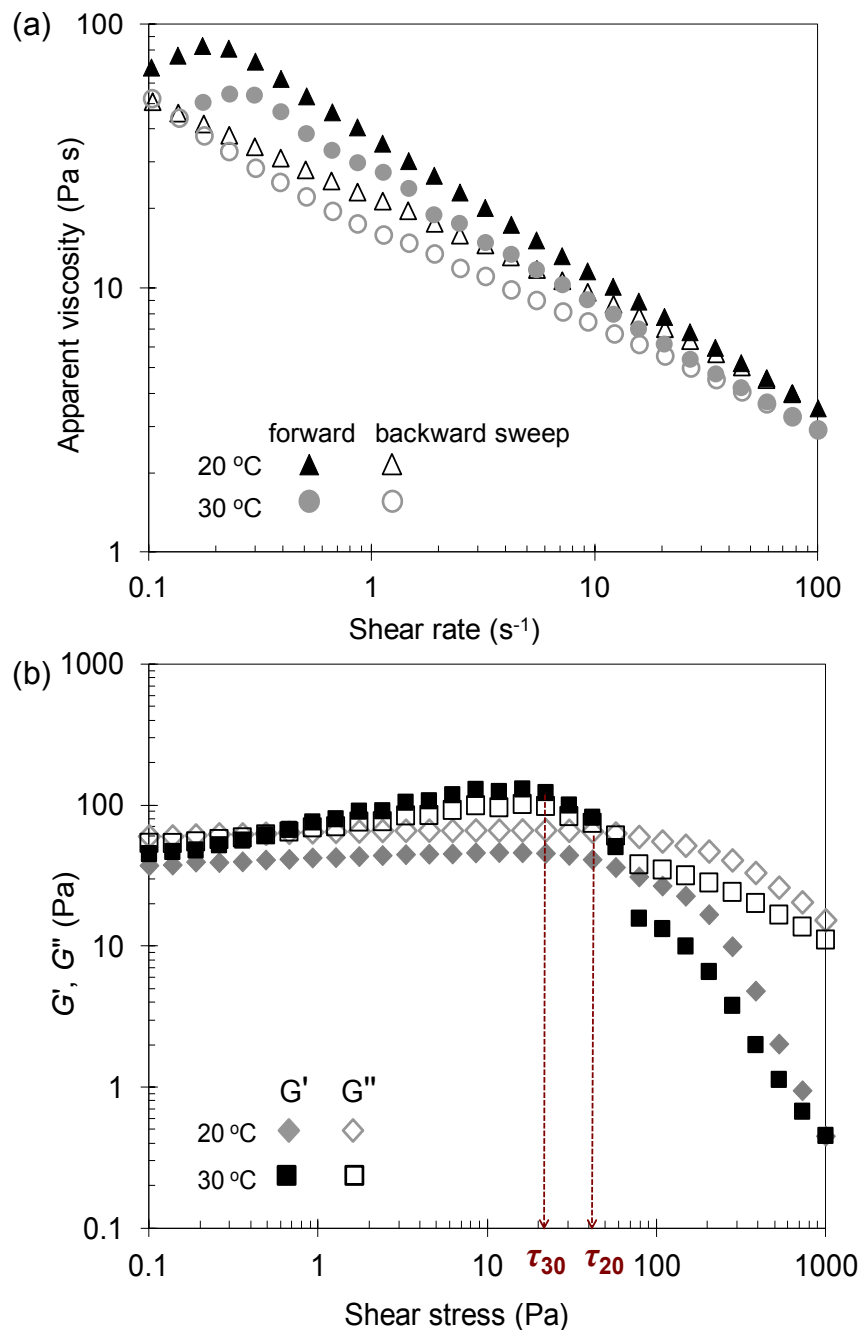


Figure 2 Rheology of 10 wt% HPC/IPA solution at 20 °C and 30 °C: (a) steady shear strain rate flow curve, (b) oscillatory stress amplitude sweeps.  $\tau_{20}$  and  $\tau_{30}$ , for 20 °C and 30 °C, respectively, is a critical stress beyond which  $G'$  decreases noticeably.

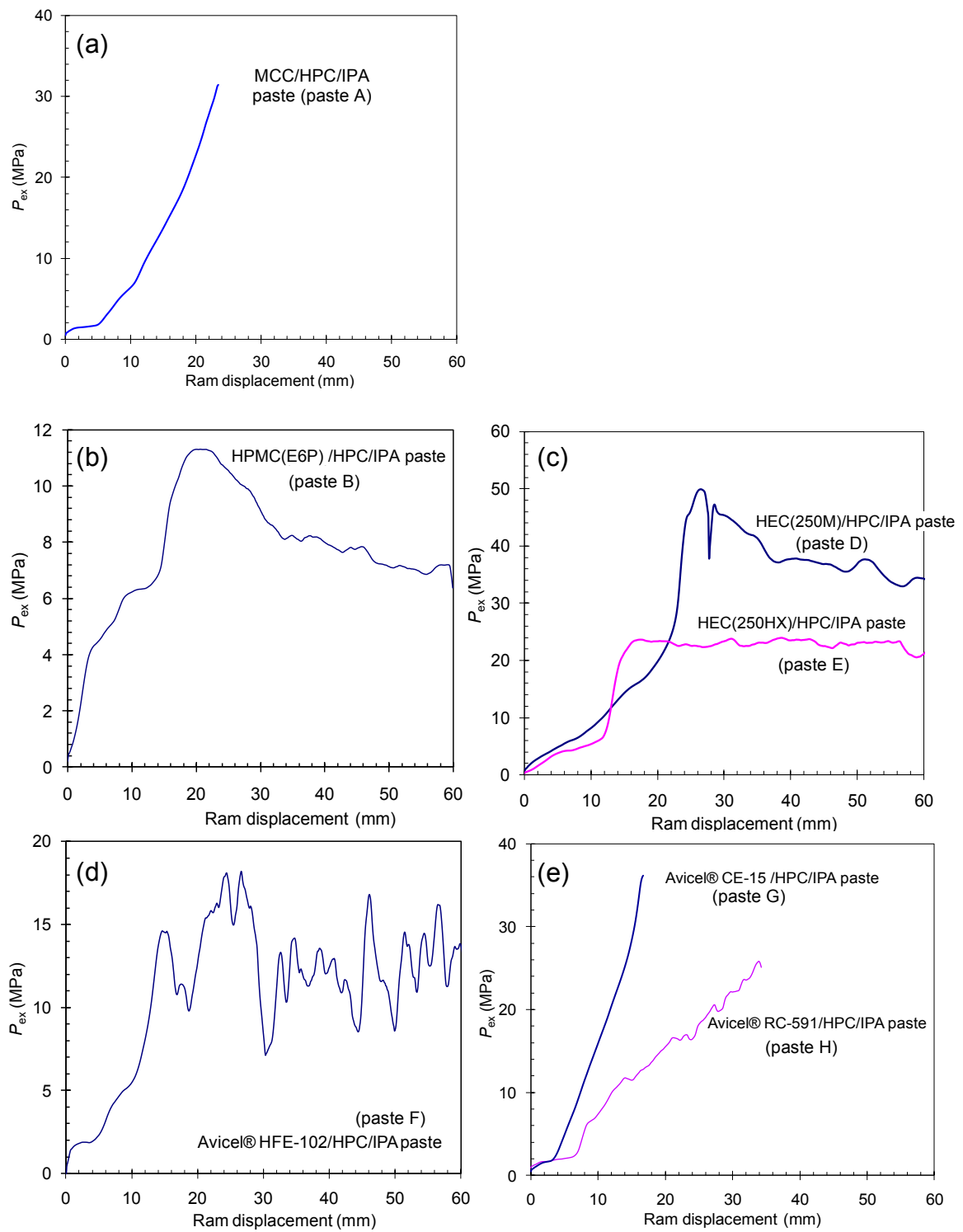


Figure 3 Ram extrusion pressure – ram displacement profiles for non-aqueous pastes using the small ram and barrel at a ram velocity of  $2.5 \text{ mm s}^{-1}$ .  $D_{sram} = 11.00 \text{ mm}$ ,  $D_{sbarrel} = 11.14 \text{ mm}$ ; Die: 7 holes,  $D = 2 \text{ mm}$  and  $L = 8 \text{ mm}$ .

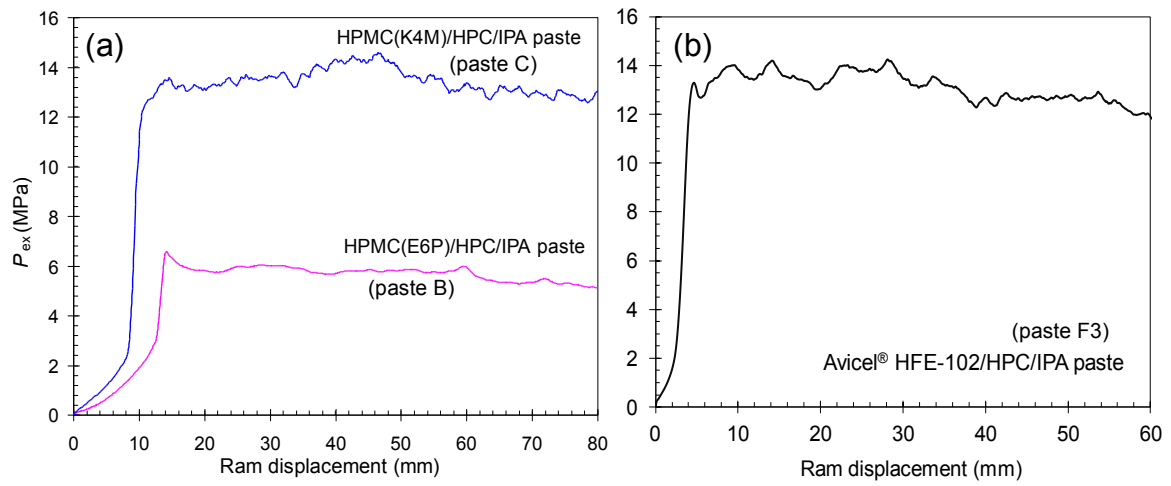


Figure 4 Ram extrusion pressure – ram displacement profile for (a) pastes B and C, and (b) paste F3 (39.3 wt% IPA) using the standard ram and barrel.  $V_{die} = 0.047 \text{ m s}^{-1}$ .  $D_0 = 25.00 \text{ mm}$ ; 33-holed die with  $D = 1 \text{ mm}$  and  $L = 2 \text{ mm}$ .

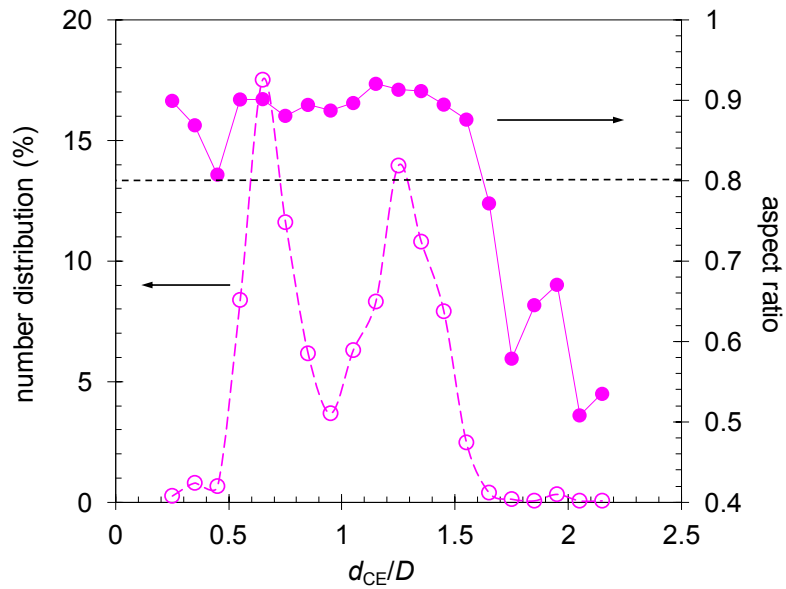
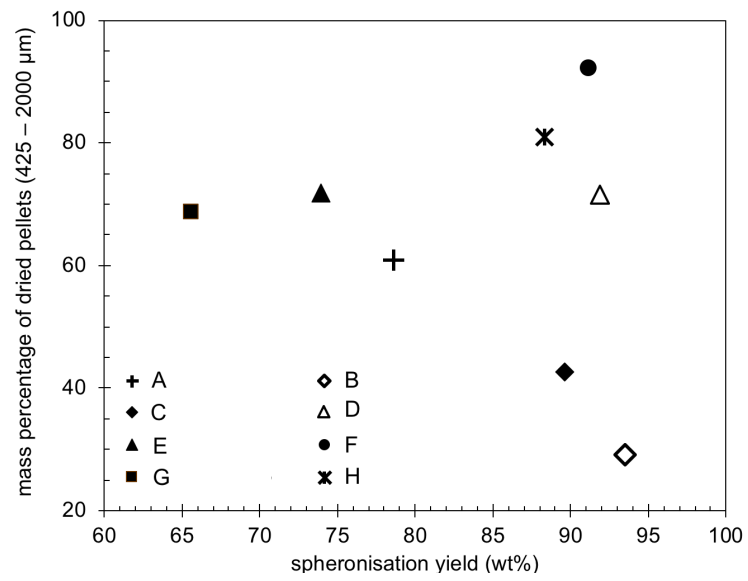


Figure 5 Pellet size and shape distribution curves from ram E-S of paste F3 (Avicel<sup>®</sup> HFE-102 NF). Symbols: open circles – number distribution, solid circles – aspect ratio. Horizontal dashed line shows the aspect ratio threshold value of 0.8. Ram extrusion parameters:  $D_{ram} = 24.82$  mm,  $D_0 = 25$  mm; 33-holed die with  $D = 1$  mm and  $L = 2$  mm;  $V_{die} = 0.047$  m s<sup>-1</sup>. Spheronisation: 30 g of extrudates, 1600 rpm for 2 min. The area under the distribution curve is normalised to a value of 10.



*Figure 6 Plot of mass percentage of dried pellets (425 – 2000 μm) against spheronisation yield (wet basis) for various pastes, labelled A to H, extruded using the LRS. 30 g of extrudates were spheronised at 600 rpm for 90 s.*

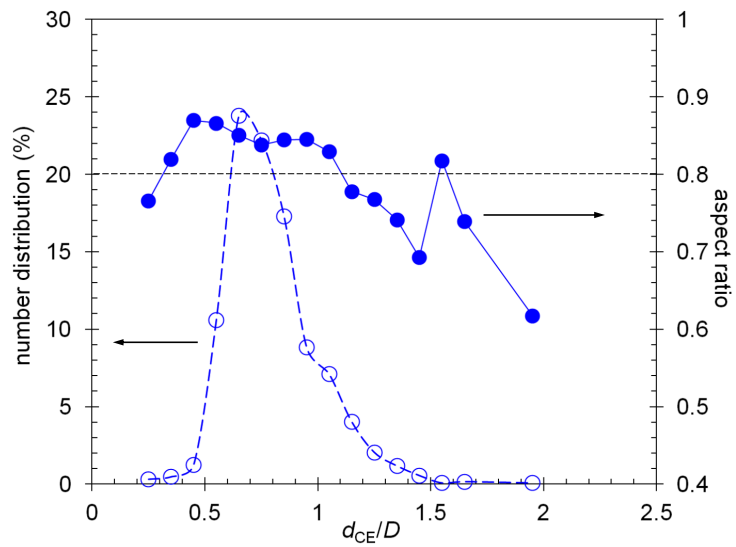
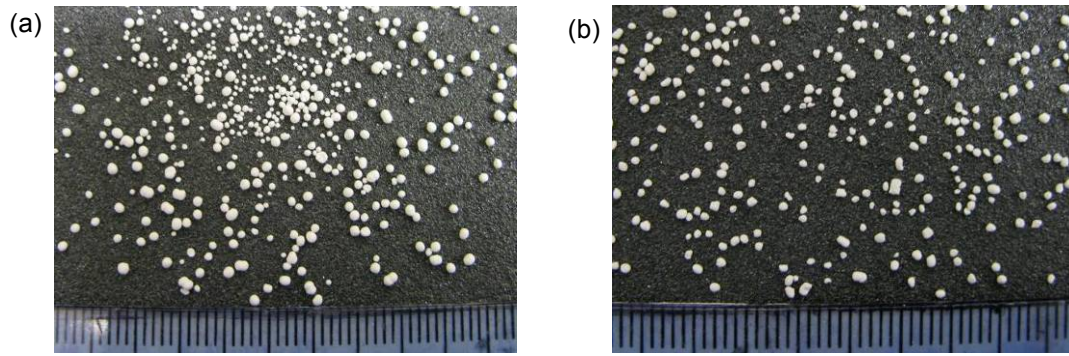


Figure 7 Pellet size and shape distribution curves after LRS E-S of paste H (Avicel<sup>®</sup> RC-591). Symbols: open circles – number distribution, solid circles – aspect ratio. Horizontal dashed line shows the aspect ratio threshold value of 0.8. LRS extrusion parameters: 8 rpm roller speed; 0.5 mm blades; 0.3 mm nip. Spheronisation: 30 g of extrudates, 1600 rpm for 3 min. The area under the distribution curve is normalised to a value of 10.



*Figure 8 Pellets prepared via (a) ram extrusion of paste API1, (b) LRS extrusion of paste API2. About 30 g of the extrudates were spheronised at 1600 rpm for 2 min. Graticule scale divisions are 1 mm apart.*

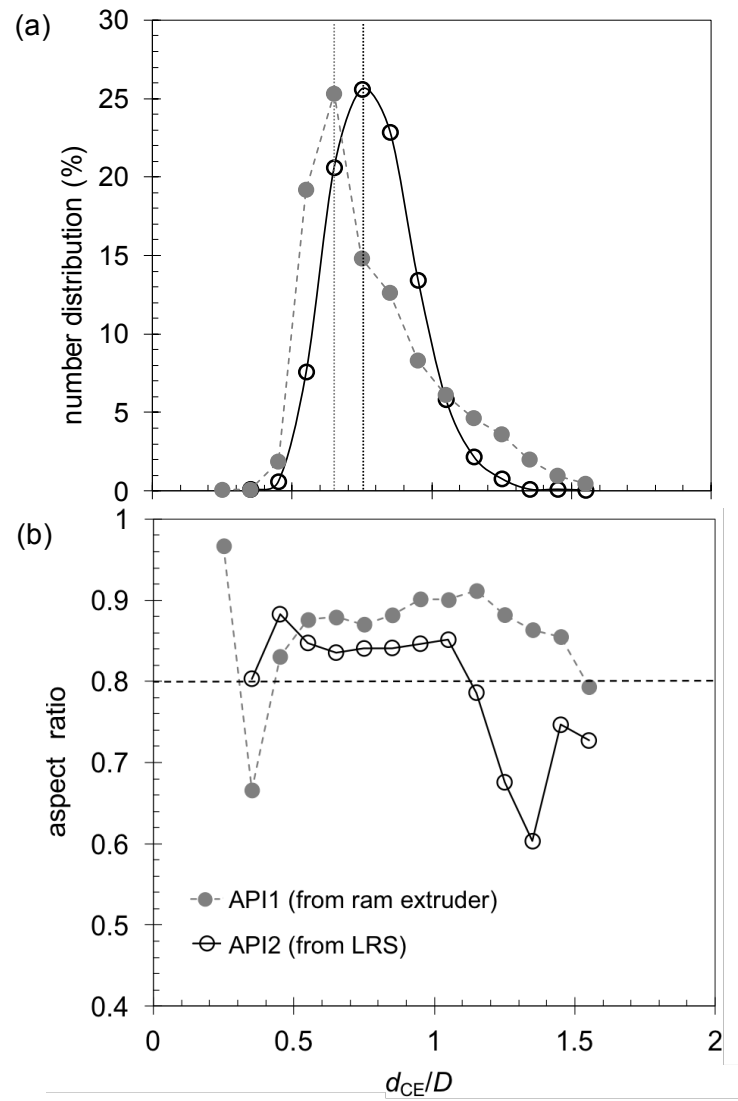


Figure 9 Size and shape distribution curves for sieved dried pellets in the size range 425 – 2000  $\mu\text{m}$  from paste API1 via ram extrusion and paste API2 via LRS extrusion: (a) number distribution; (b) aspect ratio.  $D = 1 \text{ mm}$ . Horizontal dashed line shows the minimum acceptable aspect ratio of 0.8. About 30 g of the extrudates were spheronised at 1600 rpm for 2 min. Vertical dotted lines show the mode values for the two distribution curves. The area under the distribution curves in (a) is normalised to a value of 10.