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Extrusion–spheronisation of microcrystalline cellulose pastes using a non-aqueous liquid binder

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ABSTRACT

An experimental investigation of extrusion–spheronisation (E–S) of a novel microcrystalline cellulose (MCC) formulation, comprising dimethyl sulfoxide (DMSO) as the granulating liquid, is reported. The extrusion–spheronisation performance of DMSO/MCC pastes is compared to that of similar water/MCC formulations and their rheological behaviours similarly assessed using lubricated squeeze flow. A case study involving water, DMSO and anhydrous ethanol yields important information regarding the physico-chemical properties necessary for solvents to be suitable for the extrusion of MCC.

1. Introduction

Extrusion–spheronisation (E–S) is widely used in the pharmaceutical and other sectors for manufacturing dense granules with controlled, high sphericity. In this route, the particulate solids are combined with a liquid (often referred to as the binder) to yield a dense suspension or paste which is extruded to give cylindrical extrudates which are subsequently spheronised (or *marumerised*) on a rotating friction plate (Wilson and Rough, 2006). Many active pharmaceutical ingredients (APIs) are processed as the minor components in formulations, whose processing behaviour is dominated by an excipient or filler which affords the rheological characteristics required for the extrusion and spheronisation stages. Microcrystalline cellulose (MCC) is a versatile excipient, employed frequently in E-S applications owing to its intrinsic properties when wetted with water. MCC/water pastes used in E–S are examples of soft solids, whose rheological behaviour exhibits a solid–liquid transition at a critical stress as demonstrated by Mascia and Wilson (2007). This allows the paste to be extruded, hold its shape as extrudates and be handled through the spheronisation stage.

APIs which are moisture sensitive pose challenges to conventional MCC-based extrusion spheronisation processes as a non-aqueous liquid phase is required to preserve the physico-chemical stability of the active. The selection of the appropriate liquid phase is dictated by the requirements of the API, the process and the regulatory criteria, as illustrated in Fig. 1.

Water is a well-established solvent for extrusion–spheronisation of MCC-based formulations. Comparatively few studies have reported the use of non-aqueous solvents as granulating liquids for MCC: those known to the authors are summarised in Table 1. For the majority of cases the E–S performance has often been found to be poor compared to equivalent aqueous formulations. The majority of liquids tested have been alcohols, where it was found either that spheronisation could not be achieved or the pellets crumbled to powder following drying. Millili et al. (1990) reported that pellets could be obtained with aqueous ethanol up to concentrations of 95% EtOH, but not with absolute alcohol. Similar results were reported by Schröder and Kleinebudde (1995) for isopropyl alcohol (IPA) and IPA/water mixtures.

The success of MCC–water combinations as a filler in extrusion spheronisation has been explained by two qualitative microstructural models, namely the: (i) ‘sponge’ (Fielden et al., 1988; Ek and Newton, 1998; Soh et al., 2008) and (ii) the “crystallite-gel” (Kleinebudde, 1997). These differ in the mechanism by which water is held by the MCC. In the former, most of the water is deemed to be held by the MCC as free, unbound water, *i.e.* readily lost by evaporation and free to solidify to ice upon cooling. During extrusion the MCC particles or ‘sponges’ are compressed, and the water squeezed out lubricates the inter-particle contacts, facilitating flow through the die. After extrusion, on release of the compressive stress, the

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Table 1
Reported investigations of extrusion–spheronisation featuring non-aqueous liquid phases.

Source	Solid phase	Liquid phase	Pellet quality
Millili et al. (1990)	MCC	Ethanol	Crumbled on handling
Barton et al. (1992)	Bleach activators[a]: cyclic anhydride or lactone Hydrophobic clay	White spirit	Non-friable, handled well
Schröder and Kleinebudde (1995)	MCC	IPA	Crumbled on handling
Chatlapalli and Rohera (1998)	HPMC/HEC/MCC (95%)	HPC (5%) in IPA (q.s.)	Hardness = 68 kPa friability = 0.3%
Dreu et al. (2005)	MCC	Ethanol	surface tensile strength = 0.6 MPa friability = 3%

MCC: microcrystalline cellulose; IPA: isopropyl alcohol; HPMC: hydroxypropyl methylcellulose; HEC: hydroxyethyl cellulose; HPC: hydroxypropyl cellulose.
[a] Materials not permitted for use in humans.

sponges increase in volume and the water film at the surface of the particle is reabsorbed internally, with the extrudates then appearing dry and brittle. According to this model the lubrication provided by the water expelled from the sponges is essential for extrusion.

In the crystallite-gel model, the MCC particles are deemed to be broken down by the shear forces acting on the particles during extrusion. With increasing stress the MCC is reduced to individual nano-fibrils of colloidal size, whose main effect is that to increase the contact points between the particles and generate a gel (network) which aids both extrusion and subsequent spheronisation. According to this model, reducing the MCC particle size to single colloidal fibrils is essential for the formation of the ‘crystallite-gel’, and hence to extrusion and spheronisation.

Neither of the above models consider explicitly the nature of the physico-chemical interactions between the MCC solids and the liquid, which is critical to selecting an alternative liquid phase. A starting point is that MCC swells and softens in the presence of water, indicating that the processes are related to the absorption of solvent and plasticisation (the rubber-glassy transition) observed with synthetic polymers. When an amorphous, glassy polymer (*i.e.* a stiff polymer chain which does not change shape but breaks under stress) is contacted with a thermodynamically compatible solvent, the solvent diffuses into the polymer promoting the formation of a gel swollen layer, in which the polymer is in a rubbery state (*i.e.* soft polymer which responds to a stress by changing shape). Penetration of the solvent into the polymer is therefore essential for a glassy-rubbery transition, *i.e.* plasticisation of the polymeric material.

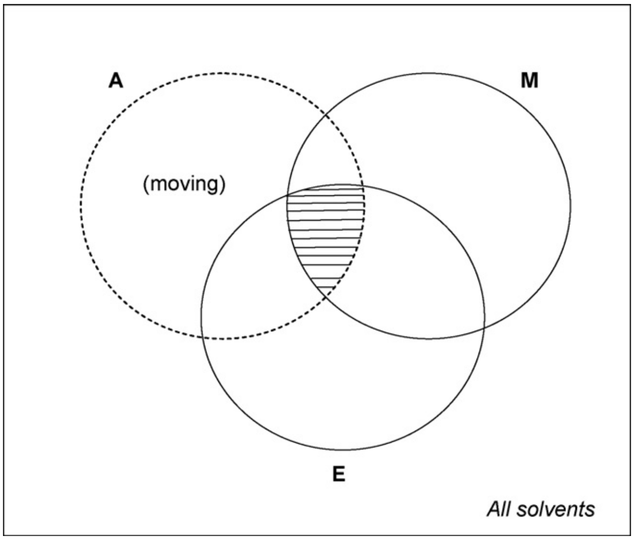

Fig. 1. Schematic of solvent selection for MCC formulations for extrusion–spheronisation: A – compatible with API; M – permitted for pharmaceutical manufacturing; E – compatible with extrusion–spheronisation. Set A is dictated by the physico-chemical properties of the API and the shaded area (union) denotes candidate solvents.

The MCC particles are fibrous rods consisting of an aggregate of interlinked micro-fibrils, and each micro-fibril contains chains of linear $\beta(1-4)$ D-glucopyranose polymer units. Mantanis et al. (1995) studied the swelling of cellulose fibres treated with different solvents and concluded that MCC fibres can swell due to a combined effect of (i) absorption into, and consequent stretching of, the micro-fibrils and (ii) absorption into the micro-fibril cell wall. In both cases absorption causes the inter-micro-fibril frictional bonds to be weakened, leading to micro-fibril separation with consequent generation of room for the solvent. Although MCC is a partially crystalline natural polymer (with ~40% amorphous regions) based on cellulose which is insoluble in water and most organic solvents, it contains many H-bond donor and acceptor groups that can be solvated by polar solvents. Strongly polar solvents like water interact strongly with MCC fibres promoting their plasticisation and extrudability. Polar solvents also promote interactions between fibres. Ek et al. (1995) used ^{13}C cross-polarisation magic angle spinning (CP/MAS) NMR to measure MCC crystallinity and showed that this increased with the addition of water. Millili et al. (1996) also hypothesised that the mechanical strength of their MCC pellets was due to conversion from intra-fibril hydrogen-bonds to inter-particle ones upon addition of water. This is likely to happen due to swelling of the MCC fibres, with consequent increase in fibre contact points as explained above. Ono et al. (1998) performed NMR relaxation studies on dilute aqueous suspensions of MCC and concluded that their high viscosity was related to a structural network formed by the MCC particles. This evidence suggests that MCC forms a weak physical gel (Rubinstein and Colby, 2003), via hydrogen-bonds between the MCC fibres when mixed with a polar solvent.

Swelling of MCC has been reported in the literature on dissolution of tablets and other solid dosage forms containing MCC. For instance, Kleinebudde (1994) measured MCC pellet sizes before and after dissolution in aqueous media and showed that swelling occurred on contact with water. Ek et al. (1995) used spin-echo NMR techniques to measure the pore sizes in beads containing MCC and reported that these swelled in a dissolving medium with a high dielectric constant (water), but not in liquid phases with low dielectric values (*e.g.* cyclohexane). Similarly, Ferrari et al. (1996) showed that during dissolution of MCC tablets in solvents such as water, methanol and isopropanol, the disintegration properties of the tablets were enhanced by higher solvent dielectric constants due to swelling of the MCC. They also reported that the penetration of the solvent into the tablet voids (spaces between the granules) was essential for swelling and consequent disintegration of the dosage form, with parameters such as liquid surface tension, γ_L, and viscosity, μ, being important in controlling this mechanism: in that (i) γ_L determines the driving force to pull the liquid into the voids, *i.e.* the capillary sucking pressure: $P_s = [\gamma_L \cos(\Theta)]/l$, where l is the characteristic void size; (ii) μ controls the rate of penetration of the liquid medium, following Darcy’s law. Solvent absorption

Table 2
Dielectric constant (ε_R), hydrogen bond donor (α^H) and acceptor (β^H) indices, surface tension (γ_L), Newtonian viscosity (μ), density (ρ) and saturated vapour pressure (P_v) of selected solvents at 20 °C (after Anslyn and Dougherty, 2006).

Solvent	ε_R	α^H	β^H	γ_L (mN m^{-1})	μ_0 (mPa s)	ρ (kg m^{-3})	P_v (mmHg)
Water	78	1.17	0.47	73	1.0	1000	17.5
DMSO	47	0.00	0.76	44	2.0	1100	0.42
Ethanol	25	0.83	0.75	22	1.2	789	43.9

into the fibres and plasticisation, *i.e.* the effect on the rheology of the MCC and its processibility, was not considered.

In their study of alcohols as liquid binders for MCC pastes, Dreu et al. (2005) considered the physico-chemical properties of anhydrous ethanol and ethanol/water mixtures, particularly liquid surface tension, dielectric constant (or relative permittivity), ε_R, and the liquid–pellet contact angle. They attributed their observations to Van der Waals and capillary forces between particles, whose importance are well known in the granulation of impermeable particles. They did not consider the effect of polarity (and hence ε_R) on the swelling behaviour and linkages between MCC fibres. The polymer literature indicates that solvents which should be able to induce plasticisation of MCC particles are ones with high polarity, high surface tension and low viscosity (as these will assist penetration of the solvent into the porous MCC fibres). Solvents with high polarity include formamide (highest), water and dimethyl sulfoxide (Anslyn and Dougherty, 2006).

In this work, dimethyl sulfoxide (DMSO) was chosen as a model solvent following the principles in Fig. 1. DMSO is, to our knowledge, not currently permitted for use in solid oral dosage forms (SODFs), although it is a class III solvent (ICH guideline) along with ethanol, acetone, *etc.* and is used in a number of pharmaceutical finished products. Water and ethanol were also used as reference solvents for MCC because spherical granules can be produced with water/MCC pastes but not with ethanol/MCC mixtures (Millili et al., 1990). Furthermore, ethanol/MCC pastes cannot be ram extruded readily, as they undergo liquid phase migration (LPM, often termed dewatering when the liquid binder is aqueous) noticeably when compressed. In contrast, water/MCC pastes only dewater under specific process conditions (Mascia et al., 2006). Solvent selection was therefore guided by dissimilarities between water and ethanol. Table 2 reports the physico-chemical properties of these three different liquid binders, which we hypothesise as explaining the differences in their extrusion–spheronisation behaviour. Formamide could be another candidate solvent in terms of properties but was not considered owing to its unacceptability (Class II solvent in ICH guideline) for pharmaceutical processing.

We demonstrate here that DMSO, a solvent with similar 'swelling' properties to water, is a suitable non-aqueous binder for E–S of MCC. The comparisons between ethanol, water and DMSO is studied at three levels, namely (a) physico-chemical characterisation of MCC–solvent pastes; (b) rheology of MCC–solvent pastes using the lubricated squeeze flow technique reported previously (Mascia and Wilson, 2007), and (c) lab-scale extrusion–spheronisation testing.

2. Material and methods

2.1. Formulation and preparation

MCC (Avivel PH101, FMC Corporation, Philadelphia) was obtained from Merck Sharp & Dohme research laboratories, Hoddesdon, England, as a fibrous particulate solid. Particle size analysis was performed using a Beckmann Coulter LS230 laser scattering device where the MCC was dispersed in water. This standard technique gave a Sauter mean size of 45 μm. Optical image analysis was also performed using a Malvern Morphologi G3 device, which yielded size and shape data (Sauter mean 71 μm, average aspect ratio 0.63). The differences in Sauter means reflect the limitations of laser sizing methods for MCC powders, which are strongly non-spherical particles and hygroscopic. Reverse osmosis (RO) water was obtained from a Millipore Elix S unit. Anhydrous ethanol (AR grade 99.99%) and DMSO (AR grade 99.99%) were obtained from Fisher Scientific.

Pastes were prepared by combining the liquid with the solids in a Kenwood KM200 planetary mixer fitted with a basket whisk. The powder was first stirred at speed 1, slowly adding liquid and then mixing for further 5 min at speed 2. The wet mass was allowed to stand for 60 min in a sealed container before use to allow equilibration. All pastes were used within 6 h of preparation. All experiments were performed at room temperature in an air-conditioned laboratory (average temperature 20 °C). Pastes were prepared on the basis of equal volume fractions of liquid addition (before absorption), as determining the volume fraction of liquid post swelling is difficult to perform experimentally and not used in practice. The formulations are summarised in Table 3: the 0.30 solid volume fraction was selected as this was known to be suitable for rheological testing such as squeeze flow (Mascia and Wilson, 2007).

It was immediately evident that ethanol interacted differently with the MCC. The MCC solids absorbed and swelled almost instantaneously in water and DMSO, but not in ethanol. The latter paste was wet to handle, whereas the former were noticeably drier. The volume of free solvent was estimated by centrifugation. Samples of paste were placed in PTFE cylinders (10 mm i.d., 20 mm height) to a height of 10 mm, and centrifuged at room temperature in a MSE Minor s device (Meadowrose Scientific, UK) at 500–4600 rpm. The PTFE containers featured a holed base (diameter ~0.8 mm) through which solvent was ejected; filter paper (Whatman, 0.45 μm pore size) was used to avoid extrusion of the pastes through the holes. The sample mass was recorded before and after testing at a given speed for 10 min. The centrifugal pressure, P_c, was estimated from (Hassler and Brunner, 1945):

$$P_c = 0.5\rho_L\omega^2\left(r_o^2 - r_i^2\right) \quad (1)$$

where ρ_L is the liquid density, ω the angular velocity, and r_i (75 mm) and r_o (85 mm) the radial distances from the axis of rotation to the inner and outer face of the sample, respectively.

2.2. Microstructure

The effect of the solvent on the microstructure of the MCC solids was investigated by mercury porosimetry, employing freeze-drying to retain the structure of the wetted solids. Paste samples were formed into short, large-base cylinders (height 20 mm, diameter 50 mm) and immersed in liquid nitrogen (−196 °C) for 30 s, then transferred to the pre-chilled shelf of a Virtis Advantage freeze drier. Samples were dried at −30 °C and 80 mTorr for four days. These conditions were not cold enough to achieve true free drying of the ethanol samples and further work on ethanol-based formulations would require a more stringent drying regime. Mercury porosimetry was performed on the dried samples using an AutoPore IV 9505 analyzer, covering a pore diameter range from approximately 5 nm to 360 μm.

Table 3
Formulations of pastes used in solvent comparison studies.

	MCC (g)	RO water (g)	DMSO (g)	Ethanol (g)	Solids mass fraction (wt%)	Solids volume fraction (ϕ)[a]
Water	150	225	–	–	40	0.30
DMSO	150	–	245	–	38	0.30
Ethanol	150	–	–	178	46	0.30

[a] Assuming no absorption.

2.3. *Rheology – squeeze flow*

The extensional behaviour of pastes is critical for extrusion and this was assessed here using lubricated squeeze flow, following the methodology reported by Mascia and Wilson (2007). Short cylindrical samples (height 25 mm, diameter 50 mm) were located between lubricated PTFE plates on a Zwick/Roell strain frame and the top plate moved downwards at a specified, constant velocity. The squeezing force was measured by a load cell and velocities ranging from 0.01–5 mm s^{-1} (corresponding to mean extensional shear rates of 0.0005–0.2 s^{-1}) tested. A detailed description of the technique and analysis is given in the earlier paper. It proved impossible to study the ethanol pastes using this technique as they behaved similarly to granular pastes with little cohesion (*e.g.* water/sand mixtures), undergoing LPM and cracking during the test. This behaviour is consistent with the lack of cohesion reported above.

2.4. *Extrusion–spheronisation*

Extrusion–spheronisation was performed on water and DMSO-based pastes with solids volume fractions (based on ingredients) of 0.38 and 0.39. Ethanol–MCC pastes could not be ram extruded for the reason explained above. The strain frame was configured to act as a ram extruder by fitting it with a piston, cylindrical barrel and dies as described by Rough et al. (2000). All surfaces in contact with the paste were stainless steel except the piston, which featured a PTFE seal to minimize leakage from the top of the barrel. Dimensions were: barrel i.d., 25 mm; die land diameter, 1 mm and various die lengths, L, to give specified L/D ratios. Square-ended dies were used. Approximately 90 g of paste was placed in the barrel and tamped down by hand, giving an initial billet height of approximately 160 mm. The paste was extruded at a constant ram velocity, V_{ram}, of 1 mm s^{-1} to avoid liquid phase migration. A total ram displacement of 100 mm was used and the mean extrusion pressure, P_{ex}, calculated from the force on the ram measured on the load cell.

Spheronisation was performed with a bench-top 120 spheroniser (Caleva Process Solution Ltd., Dorset, UK) featuring a 120 mm diameter cross-hatched friction plate (3 mm pitched truncated square pyramids, 1 mm high). Approximately 60 g of extrudates were spheronised for 5 min at a rotational speed of 1500–1600 rpm, and the resulting pellets dried in a vacuum oven (Gallenkamp, Thermo ARL UK) at 201 mbara. The temperature and time of drying for the different formulations were 70 °C for 18 h (water based), and 120 °C for 40 h (DMSO based). These drying conditions were not optimised as the aim for this work was to obtain pellets suitable for further testing. The residual solvent contents were not measured as DMSO is not currently permitted in SODFs.

Pellets were viewed optically using an Intel® Play™ QX3™ microscope (Mattel, California) and their shape and size distribution quantified using a Canty SolidSizer (JM Canty SolidSizer, Inc., Lockport, NY). Dry pellets were placed on a vibrating tray from which they flowed freely under gravity past a digital camera into an aluminium bowl. One thousand individual pellet digital images were recorded and processed to yield the particle perimeter, minor and major axes. The latter parameter was used as a representative dimension of the pellets.

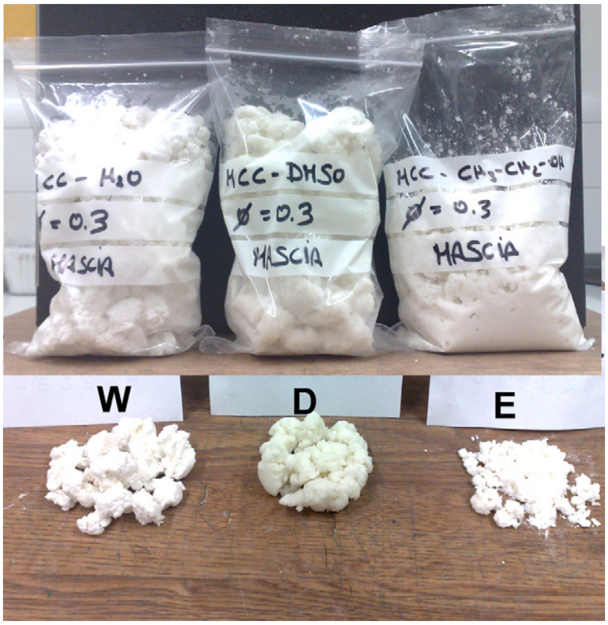

Fig. 2. Photographs of MCC/solvent pastes mixtures: W – water, D – DMSO, and E – ethanol.

2.5. *Tabletting*

The mechanical strength of the pellets was evaluated by compacting them into tablets as described by Murray et al. (2007). Approximately 0.9 g of pellets were poured into a stainless steel cylindrical compaction die (i.d. 10 mm, height 15 mm) and compressed with a stainless steel punch attached to the crosshead of the strain frame at a velocity of 0.1 mm s^{-1} up to a maximum load of 15 kN (∼190 MPa). The degree of compaction, γ, was calculated

Fig. 3. Cylinders of water, DMSO and ethanol/MCC pastes after freeze-drying. The ethanol cylinder did not preserve the formed shape and crumbled back to powder during handling.

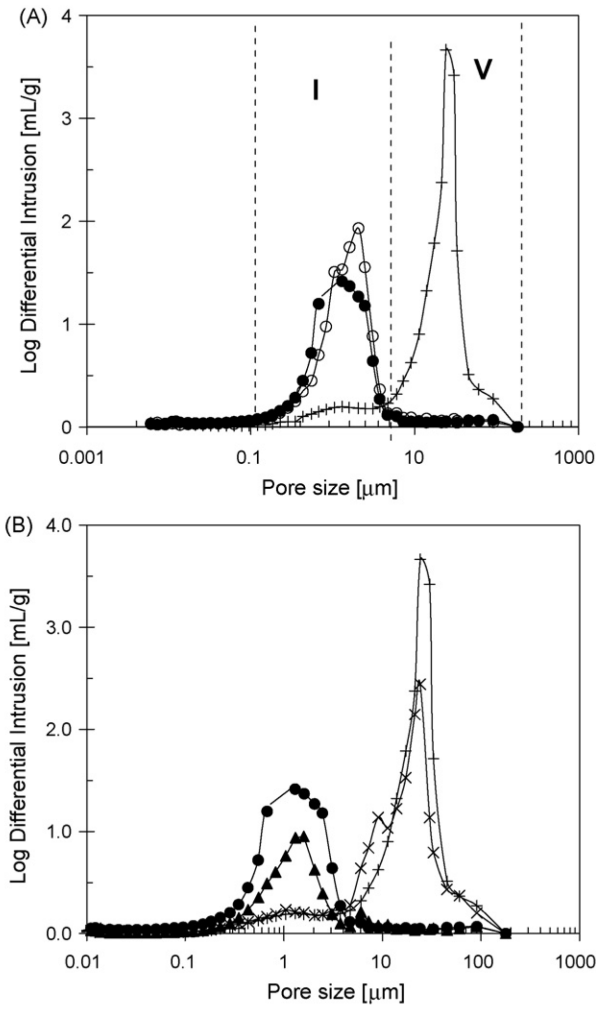

Fig. 4. MCC pore size distributions obtained from mercury porosimetry of dry powder (+) and $\phi = 0.3$ pastes following freeze drying: (a) (●) – after mixing with water; (○) – after mixing with water and squeeze flow testing: (b) after mixing with (×) – ethanol; (▲) – DMSO; (●) – water.

from (Santos et al., 2005):

$$\gamma = 100\frac{\rho - \rho_0}{\rho} \tag{2}$$

where ρ and ρ_0 are the apparent density of the tablet at maximum and zero compaction pressure, respectively. The mechanical strength of the tablets was estimated by measuring the tensile crushing strength, σ_t, as described by Newton et al. (1971). Each cylindrical tablet was positioned co-axially between two emery paper-coated stainless steel platens which approached each other at constant speed of 0.1 mm s^{-1}, for a total displacement of 4 mm. The tensile crushing strength was calculated from:

$$\sigma_t = \frac{2F_{\max}}{\pi D h} \tag{3}$$

where $F_{\max}$ is the force at failure, and D and h are the initial diameter and the height of the tablet, respectively.

3. Results and discussion

3.1. Microstructure

The effect of solvent absorption into MCC fibres with consequent swelling was evident in preparation (Fig. 2): for the same solid volume fraction the water and DMSO pastes occupied a larger volume than the ethanol formulation. The cohesion of the water and DMSO pastes was retained on drying, whereas the ethanol block collapsed to powder on handling, as illustrated in Fig. 3. It is evident that water and DMSO promote solid structure formation, *i.e.* direct interactions among the different MCC fibres as also reported by other workers, and discussed above. Contrarily, ethanol does not promote these interactions.

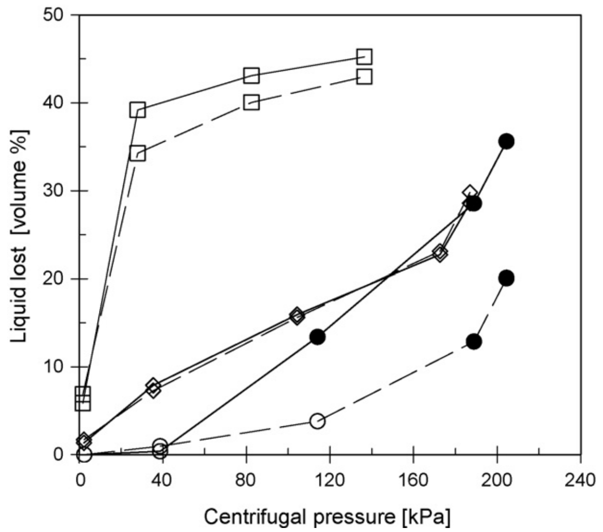

Fig. 5. Centrifugation of MCC pastes ($\phi = 0.3$) prepared with ethanol (squares), water (diamonds) and DMSO pastes (circles). Dashed loci – filter paper, continuous loci – without filter paper. Solid circles indicate pressures at which the DMSO paste was found to extrude through the holes of the filter container.

Fig. 4(a) shows that the pore size distribution in MCC fibres changed following contact with water. The dry powder exhibits a bimodal distribution, with a dominant peak around 20 μm, labelled (V), associated with voids between particles (consistent with the Sauter mean particle size ~45 μm). A smaller fraction of intra-particle voids is evident between 1 and 10 μm, labelled (I), which is associated with small pores between the micro-fibrils. Following contact with water, swelling of the individual MCC particles reduces the spaces between them (causing the inter-particle voids to disappear), and there is also a noticeable increase in the (I) fraction. This swollen state was retained even after squeeze flow

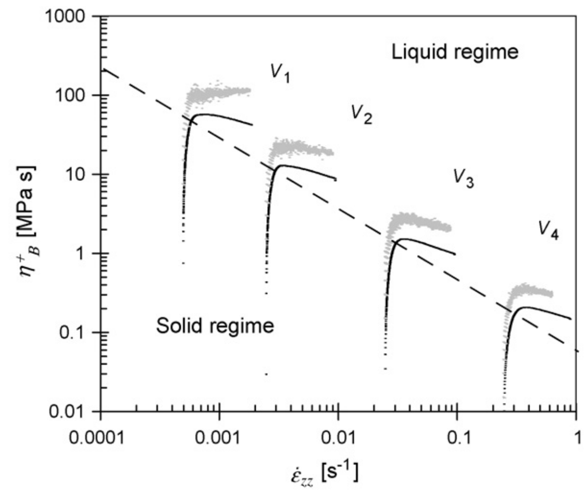

Fig. 6. Constant velocity squeeze flow testing with lubricated PTFE plates for $\phi = 0.30$ pastes. Squeezing velocities: V_1, 0.01; V_2, 0.05; V_3, 0.5; V_4, 5 (all in mm s^{-1}). Biaxial stress growth coefficient *vs.* axial strain rate; black profiles – DMSO; grey – water. Dashed loci indicate flow onset stress, separating solid from liquid flow regimes.

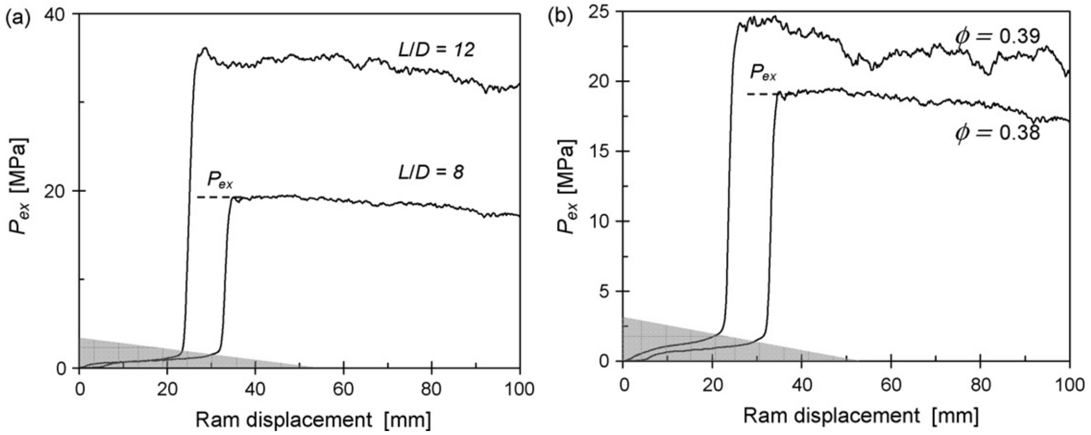

Fig. 7. Extrusion pressure (P_{ex})-displacement profiles for ram extrusion of DMSO/MCC pastes at $V_{ram} = 1\ mm\ s^{-1}$: (a) effect of L/D, with $D = 1$ mm; (b) effect of solids volume fraction. Grey region indicates initial compaction before the onset of flow.

testing, where the matrix was subjected to a total stress of around 20 kPa. This result, together with the observation that MCC particle sizes did not change noticeably on squeeze flow testing, indicate that the sponge model – albeit a rubber sponge picture – is more appropriate for the MCC interaction with water. These results are consistent with the observations of Soh et al. (2008), who classified their pore size distributions into two types, as either greater than or less than 10 μm. They observed that the wet massing consistency of six different MCC grades correlated strongly with the amount of small pores present in the native powder. They did not measure pore size distributions following contact with the liquid binder, and did not consider liquids other than water.

The porosimetry profiles in Fig. 4(b) confirm the effect of polarity. The DMSO profile resembles that of water, whereas the ethanol profile is almost identical to that of the dry MCC powder. Ethanol, which has a lower surface tension (reduced penetration) and polarity (unfavourable interaction) than the other two solvents, does not induce any microstructural rearrangement. The voids between the particles are unchanged and therefore filled with ethanol which is consistent with its wet appearance and inability of this paste

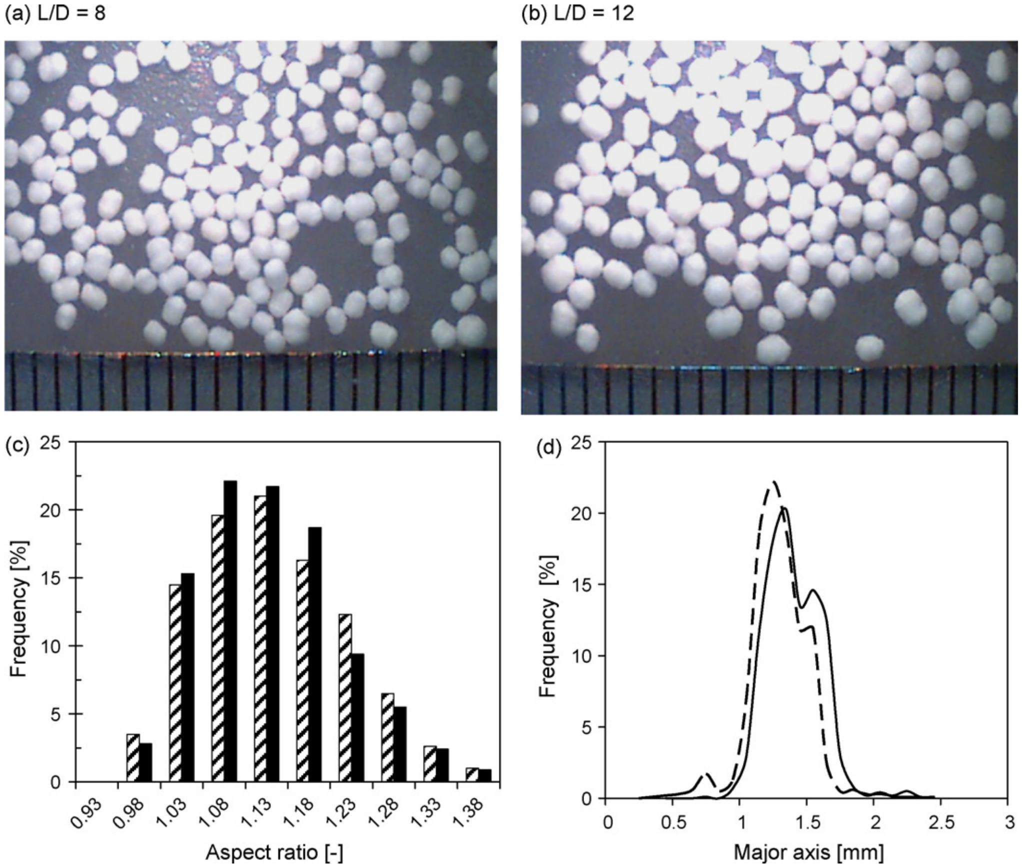

Fig. 8. Spheronised pellets generated from $\phi = 0.38$ MCC–DMSO pastes, extruded at $V_{ram} = 1\ mm\ s^{-1}$ through $D = 1$ mm dies. Extrudates were spheronised at ~1550 rpm for 5 min. (a) and (b) show micrographs of pellets obtained from $L/D = 8$ and 12, respectively (ruler divisions 1 mm apart); (c) shape and (d) size distribution; shaded bars and dashed lines indicate $L/D = 12$.

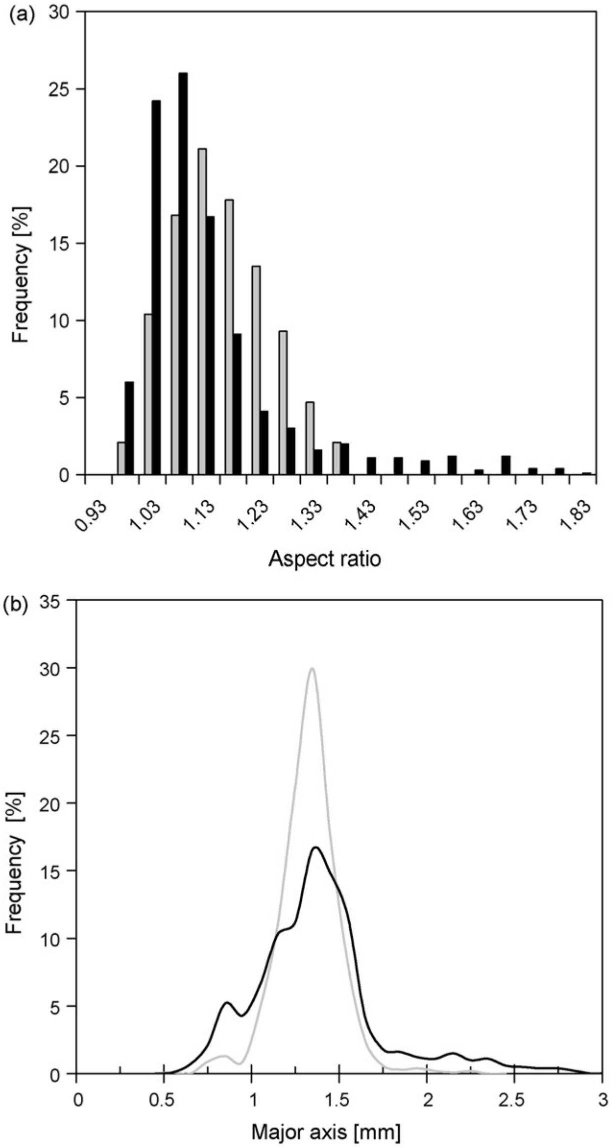

Fig. 9. Size and shape distributions of pellets obtained from ram extrusion–spheronisation [$L/D = 8/1$, $V_{\mathrm{ram}} = 1\ \mathrm{mm\,s^{-1}}$] of MCC–DMSO pastes (grey profiles) and screen extrusion–spheronisation [10 rpm] of MCC–water pastes (black profiles). $\phi = 0.39$.

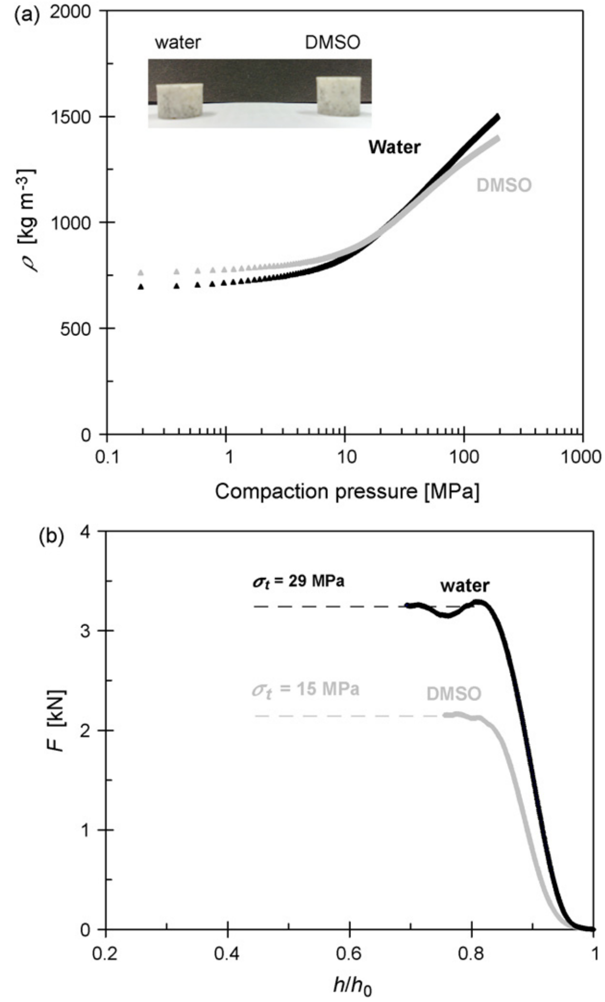

Fig. 10. Comparison of (a) pellet compaction profiles and (b) crushing tests for water (black loci) and DMSO (grey loci) tablets. Image insert in (a) shows tablets. Dashed lines in (b) indicate force at failure, used to calculate σ_t.

to hold much liquid. The opposite is observed for DMSO, which exhibits the same result as water. However, fewer pores (I) are formed with DMSO than water, suggesting that DMSO might not penetrate the spaces between the micro-fibrils as readily as the water [$\gamma_{L,\mathrm{DMSO}} < \gamma_{L,\mathrm{DMSO}}$ (Table 2)].

The affinity between MCC and polar solvents is confirmed by the centrifugation testing reported in Fig. 5. Approximately 40% of the ethanol was lost on centrifugation at low speed, indicating that this amount of solvent occupied the larger particle voids and was free to move through the matrix. The remaining 60% could be attributed to liquid held in the small pore fraction (I) with a long permeation path, or liquid held at particle contacts by capillary forces. The amount of liquid loss increased gradually with extended centrifugation time, confirming this hypothesis (data not reported). In comparison, both water and DMSO are retained more strongly by the MCC fibres which suggest that the liquids occupy the small pore fraction (I). These results are consistent with the pore size distribution of the MCC pastes measured by the mercury porosimetry analysis (Fig. 4).

The figure also shows that MCC retains DMSO more strongly than water, which can be related to this solvent being able to form stronger H-bonds than water and having a lower cohesive energy than water, allowing it to be absorbed more readily into the polymer matrix (Mantanis et al., 1995). Zakharov et al. (2006) reported that cellulose absorbs DMSO preferentially when wetted with mixtures of equal mole fractions of water and DMSO. This was confirmed by measuring the MCC solid density after freeze-drying: only the MCC treated with DMSO showed a significant reduction in density compared to the dry MCC (giving a density of $1460\ \mathrm{kg\,m^{-3}}$ *cf.* $1530–1540\ \mathrm{kg\,m^{-3}}$ for MCC powder and other pastes). This indicates that DMSO can be absorbed *into* the solid polymer or micro-fibrils, whereas water is probably only absorbed in the micro-fibril cell wall. The observation that the MCC–DMSO pastes seeped through the retaining grid indicates that the material is softer than the MCC–water paste, which is consistent with stronger absorption.

The softness (lower viscosity) of the DMSO paste was confirmed by the squeeze flow testing summarised in Fig. 6. The testing mode, with lubricated plates promoting wall slip, allows extensional deformation to be studied. The material initially undergoes a compression (solid-regime behaviour) before flowing steadily outwards, as discussed by Mascia and Wilson (2008). Fig. 6 shows that the extensional viscosity (the biaxial stress growth coefficient), η_B^+, increases rapidly with local extensional shear rate, $\dot{\varepsilon}_{zz}$, in the solid regime and then exhibits shear-thinning behaviour. The DMSO data are plotted alongside those obtained for water and exhibit two noticeable features. Firstly, the extensional viscosity for the former is consistently lower than the water-based paste, even though the viscosity of liquid DMSO is greater than that of water, indicating that the DMSO has softened the MCC fibres to a greater extent. Secondly, the DMSO paste exhibits similar shear-thinning behaviour (characterised by a power law index, n, of $\sim$0.5) across the whole range of velocities tested, whereas water exhibits a mild degree of shear thickening at the lowest velocity. The latter effect is associated with liquid phase migration and its absence with the DMSO paste is further confirmation of the affinity of MCC for DMSO.

3.2. Extrusion–spheronisation

Ethanol–MCC pastes could not be readily formed into cohesive masses and could not be extruded using liquid contents known to give good E–S results for water–MCC pastes. In contrast, DMSO pastes could be readily extruded as indicated in Fig. 7. The extrusion pressure, P_{ex}, increased with solids content and L/D, as reported for MCC–water and other pastes (*e.g.* Rough et al., 2000). Water-based MCC pastes exhibited higher extrusion pressures than the corresponding DMSO pastes, as also observed during squeeze flow testing (Fig. 6). The unsteady P_{ex}–time profile for $\phi = 0.39$ (Fig. 6(*b*)) was accompanied by gross circumferential fracture in the extrudate, but this did not prevent the material from being successfully spheronised (see Rough and Wilson, 2005).

Both DMSO paste formulations yielded extrudates which could be spheronised successfully. The data presented for $\phi = 0.38$ in Fig. 8 show well-rounded pellets with acceptable size and shape distributions. A fraction lay above the limiting aspect ratio of 1.2 required for reproducible coating and reliable controlled release suggested by Chopra et al. (2002). There is, however, considerable scope for optimisation of both the extrusion and spheronisation conditions to reach this target, as reported extensively in the literature (*e.g.* Newton, 1994; Kleinebudde et al., 1999).

The mechanical strength of the DMSO pellets was assessed by compaction and tablet breakage, alongside MCC–water pellets generated on a laboratory basket-screen extruder (Caleva model 25) with 1 mm hole diameter. The screen extruder was in regular use for pharmaceutical studies so ram extrusion was used to generate the DMSO pellets rather than commit the extruder to de-contamination and re-registration. Identical liquid contents ($\phi = 0.39$) were used and pellets were oven dried before compression, yielding almost similar size and shape distributions although some differences were evident (Fig. 9). The water-based pellets had an aspect ratio closer to 1 but a slightly wider size distribution than the DMSO pellets, and this was considered acceptable for this comparison, particularly because the DMSO route had not been optimised.

Granules produced by extrusion–spheronisation can be used in various applications, including mainly encapsulated products but also tablets. The former require the granules to be coated uniformly before filling, whereas the latter also often require particular compression behaviour. Both the water and DMSO-based formulations yielded acceptable tablets. The compaction profiles presented in Fig. 10(a) follow a similar trend, with a granule yield point in both cases lying around 12 MPa. The final compressibility is slightly different, at 49% for DMSO at 200 MPa *cf.* 58% for water, which is reflected in the heights of the tablets in the inset. The difference in compressibility can be readily explained as the DMSO pellets have a slightly narrower size distribution and are less spherical than the water pellets, therefore resisting compaction. Murray et al. (2007) used the same apparatus and reported a granule yield point of 17 MPa for MCC–water pellets of similar composition but a size fraction of 1–1.18 mm, *cf.* 1.3 mm used here. The similarity in mechanical strength, despite the use of different liquids, indicates that the dried MCC solids are in a similar state. This is consistent with the microstructure results and confirms that DMSO, as a polar solvent, interacts with MCC in a similar fashion to water.

The tensile crushing strengths obtained from tests such as those presented in Fig. 10(b) showed consistently lower σ_t values for the DMSO tablets, which is related to the pellets having higher resistance to compaction. Similar relationships between the mechanical properties of the pellets and their tabletting behaviour were reported by Johansson et al. (1995) for pellets obtained by extrusion–spheronisation of MCC pastes prepared with water/alcohol mixtures as binder.

4. Concluding remarks

The physico-chemical properties which render a solvent suitable for the extrusion–spheronisation of MCC have been investigated and DMSO identified as an alternative model solvent. DMSO–MCC pastes could be successfully processed into spherical pellets, dried and compressed into tablets with mechanical strength similar to equivalent water formulations. Further optimisation of DMSO formulations and processing parameters is anticipated to yield pellets and tablets with properties matching those achievable with MCC–water formulations. This was not considered here as DMSO is not currently permitted in SODF applications.

Polarity, surface tension and viscosity were identified as critical properties. Polarity relates to the interactions of the solvent with the MCC fibres, whereas surface tension determines the driving forces for penetration of the solvent into the MCC fibre pores, and viscosity the rate at which penetration occurs.

Penetration of the favourable solvents (water and DMSO) induced swelling of MCC particles, with behaviour consistent with that reported by Mantanis et al. (1995): (i) absorption of the solvent into the cellulose micro-fibrils (DMSO), promoting stretching of the micro-fibril units with formation of additional pores for the solvent; and (ii) absorption of the solvent into the micro-fibril cell wall (water). In both cases the solvent is held in small pores within the MCC fibre, enhancing the capacity of the MCC to physically retain the liquid phase during extrusion and subsequent spheronisation. The softer nature of the DMSO/MCC pastes (as indicated by squeeze flow testing) was attributed to penetration of the DMSO into the polymer. The absence of liquid phase migration in DMSO pastes at low testing speeds also indicated a stronger interaction than with water.

Ethanol, in comparison, exhibits a lower polarity than both water and DMSO so does not solvate the MCC polar groups and does not promote microstructural rearrangement in MCC. A significant fraction of the ethanol was retained in the large inter-particle voids and could be readily removed by compression or centrifugation.

It is known that MCC fibres swell when contacted with thermodynamically compatible solvents undergoing a glass-rubber transition (*i.e.* plasticisation). This phenomenon has been studied extensively in the area of synthetic polymers and protein gels (see Rubenstein and Colby, 2003). Swelling of the MCC fibres causes a reduction in the size and volume of inter-particle voids, bringing fibres together which facilitates the formation of inter-particle hydrogen-bonds: MCC was found to form a mechanically stable structure when wetted with water or DMSO but not with ethanol. Furthermore, the pore size distribution of this structural network, which physically retains the solvent within its small pores, was unmodified after squeezing, indicating that no particle breakage occurs during the process. This suggests that the microstructural rearrangement in MCC induced by highly polar solvents not only includes the formation of new pores for the solvent to penetrate but also the interaction between the different fibres (*i.e.* inter-particle bonds). These changes are consistent with the description of Mantanis et al. (1995), of micro-fibrils tending to align into better defined (crystal) structure. We suggest that upon swelling the MCC fibres forms a weak physical gel whose porous structure acts as a sponge which can retain large amount of liquid. The wet MCC could then be justifiably described as a 'jelly-sponge'.

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