Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 350 (2008) 145–154
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

The evaluation of modified microcrystalline cellulose for the preparation of pellets with high drug loading by extrusion/spheronization

F. Podczeck [a,*], P.E. Knight [b], J.M. Newton [b]

[a] *School of Health, Natural & Social Sciences, Pasteur Building, City Centre Campus, Sunderland University, Sunderland SR1 3SD, UK*
[b] *The School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, UK*

Received 17 June 2007; received in revised form 21 August 2007; accepted 24 August 2007
Available online 31 August 2007

Abstract

The performance of microcrystalline cellulose (MCC) which had been modified by the inclusion of various levels of sodium carboxymethylcellulose (SCMC) in the wet cake prior to drying, in terms of their ability to form pellets by a standardised extrusion/spheronization process has been assessed. Initial screening of the ability of the modified MCCs to form pellets with an 80% level of lactose as a model drug identified two potential products containing 6 or 8% of SCMC (B 6 and B 8). These two products were compared with a standard grade of MCC (Avicel PH101) in terms of their ability to produce pellets with 80% of model drugs of low (ibuprofen), intermediate (lactose) and high (ascorbic acid) water solubility when subjected to a standardised extrusion/spheronization process. Also assessed was their ability to retain water with applied pressure using a pressure membrane technique and their ability to restrict water migration during extrusion with a ram extruder. The two new types of MCC (B 6 and B 8) were able to form good quality pellets with all three model drugs, whereas Avicel PH101 could not form pellets with this high level of ibuprofen. This improved performance was related to the ability of the new types of MCC to hold higher levels of water within their structure and restrict the migration of water in the wet mass when subjected to pressure applied during the process of preparing the pellets. There is evidence to show that the two new types of MCC can function over a wider range of water contents than Avicel PH101 and that they have an improved performance if the extrusion process is rapid and if, after incorporation of the water into the powder, the sample is stored for some time before extrusion.

Keywords: Extrusion/spheronization; High drug loading; Modified microcrystalline cellulose; Pellets

1. Introduction

The ability to produce pellets with a high drug loading is one of the claimed advantages of the process of extrusion/spheronization (Reynolds, 1970). As yet it is not possible to achieve high drug loading with all drugs, as it has not yet been possible to identify a universal excipient which could achieve such an outcome nor identify the property of drugs which controls the ability to achieve acceptable pellets with existing excipients. Thus even for a series of closely related esters of benzoic acid, it was not possible to achieve high drug loads with the PH101 grade of microcrystalline cellulose (Tomer et al., 2002) for all the compounds tested. In some instances this was associated with the inability to extrude the mixtures of drug, excipient and water (Tomer et al., 2001a), while in other cases, it was associated with the inability to form pellets from extrudate (Tomer et al., 2002). There have been reports which provide evidence for the ability to prepare pellets with up to 80% loads of additives using Avicel PH101, e.g. Bains et al. (1991), Yuen et al. (1993) and MacRitchie et al. (2002). Podczeck and Knight (2006) were able to show that the inability of Avicel PH101 to function with a 80% content of a water insoluble drug, ibuprofen, was associated with the migration of the water within the formulation during extrusion rather than a range of rheological parameters measured by capillary rheometry. Both lactose and ascorbic acid at the same level of 80% showed some water migration, yet satisfactory pellets could still be produced. There is one report of glyceryl monostearate at 10% producing satisfactory pellets with diclofenac sodium, but none of the three other drugs in the study formed pellets with this excipient unless microcrystalline cellulose was also present and even then, not above 60% of drug (Chatchawalsaisin et al., 2005). Hileman et al. (1993a,b) reported that the colloidal grade of Avicel RC 591 could be used to produce pellets with levels of a model drug up to approxi-

* Corresponding author. Tel.: +44 191 515 2568; fax: +44 191 515 2568.
E-mail address: fridrun.podczeck@sunderland.ac.uk (F. Podczeck).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.08.040

mately 80%. Unfortunately they evaluated the roundness by a procedure which is not a very sensitive method to determine the shape of pellets (Chapman et al., 1988). Hileman et al. (1993b) defined a "roundness parameter", which is identical with the circularity shape factor first reported by Cox (1927), and which Hileman et al. thus should have cited as such. The limits of sensitivity of this shape factor are clearly defined by Cox in the original article and leave no doubt that the use of it to determine a difference from being round is difficult. Hileman et al. reported values which clearly indicated that the pellets were only rounded rather than close to sphericity. Despite this, they made claims to an adequate quality of shape of the pellets based on their ability to fill into hard gelatin capsules by hand. Chopra et al. (2002), however, have shown that the reproducible filling of hard gelatin capsules by machine is possible with pellets of aspect ratios as high as 1.2, which are clearly very far from round. The results that are provided by Hileman et al. (1993a,b) do not, therefore, provide clear evidence of the ability of RC 591 to produce round pellets with high drug loads. Poor assessment of the pellet shape also limits the claims for the benefits of the use of the RC 591 grade for high drug loading made by O'Connor and Schwartz (1984). There was no assessment of pellet shape by Jalal et al. (1972) and Malinowski and Smith (1975), who used the RC 581 grade of Avicel in their formulations. They were mainly concerned with producing granules for tabletting rather than pellets for general use and did not seem to consider shape as a necessary characterisation. Newton et al. (1992) were able to show that all the colloidal grades of Avicel (RC 501, 581, 591 and CL 611) when mixed with an equal weight of lactose, for a range of water levels, produced very smooth extrudate, but the pellets they produced were 'rounded' rather than 'round'. If pellets cannot be produced with 50% lactose, these grades are unlikely to function with higher levels of active. The tendency of the existing sodium carboxymethylcellulose containing microcrystalline cellulose (MCC) grades to form sticky granules in preparing pellets by extrusion/spheronization was part of the justification for the preparation of new grades of MCC in the patent of Erkoboni et al. (1998).

Clear differences in the rheological characteristics of wet masses prepared from powdered and colloidal grades of Avicel, mixed with an equal quantity of lactose have been demonstrated by Raines et al. (1990) and Chohan and Newton (1996). Avicel RC 591 and an experimental grade, Avicel 955, however, were found to have higher water retention capacities than those of the PH101, 102 and 105 grades of Avicel when assessed by a centrifuge technique (Tomer et al., 2001b). This may have implications for their function in the process, where the retention of water in the wet mass is important both at the extrusion and the spheronization stage.

Avicel 955 was found to be capable of forming satisfactory round pellets with a range of 16 model drugs at an 80% level (Jover et al., 1996). Although the drugs were selected to represent a range of drug properties, such as pK_a, freezing point depression and solubility, none of these properties could be readily quantitatively related to the properties of the pellets. It was, however, found possible to predict the best water content to use in a formulation for 50% of the formulations with a non-linear model between the drug properties selected and the water content. Thus modification of the microcrystalline cellulose does appear to offer a possible way forward.

Battista (1971) describes the preparation and properties of MCC. It is clear that there are numerous variables in the process resulting in MCC with different characteristics and properties. A series of modified products of MCC, which have been produced by the FMC Corporation, were supplied for this study. They will be assessed, in particular, for their ability to retain water during the extrusion process, where long dies will be used rather than short dies of the screen extruder. This approach provides the ability to measure the forces needed to extrude the wet mass and a method of assessing the water retention capacity of a formulation, which is important both at the extrusion and the spheronization stage. In the former, water migration can result in variable levels of water in the extrudate, while in the latter stage it can result in the migration of water to the surface of the pellets during rotation on the plate, producing agglomeration of the pellets.

2. Materials and methods

2.1. Materials

Two series of modified MCC were produced by FMC, Philadelphia, USA. The batches of the 'A' series are based on the 'wet cake' associated with the manufacture of the Avicel PH grades. The wet cake is the aqueous dispersion of MCC produced by hydrolysis of cellulose prior to the spray-drying stage. The batches of the 'B' series are based on the 'wet cake' used to produce the RC grades of Avicel. In both cases various quantities of sodium carboxymethylcellulose (7LF grade) were added to the wet cake and the system spray dried to produce a dry powder. The 7LF grade of sodium carboxymethylcellulose is one in which there is an average of 0.7 hydroxyl groups substituted out of the three per anhydroglucose units of the polymer chain, and it is a low viscosity food grade. This contrasts with the normal RC 591 grade, which contains a medium viscosity grade sodium carboxymethylcellulose, i.e. 7MF. Avicel PH101 (FMC, Philadelphia) was used as a control in the study. The details of some properties of this grade of MCC and the experimental types of MCC which were manufactured by FMC (Philadelphia, PA, USA) are presented in Table 1.

The model drugs were European Pharmacopoeia grade, ascorbic acid (Sigma Chemical Co., St. Louis, USA), ibuprofen 50 (Boots Pharmaceuticals, Nottingham, UK) and lactose α-monohydrate, impalpable grade (Sheffield Chemical Products, Norwich, NY, USA). The volume mean particle size of the drugs, determined in a suitable non-solvent by laser diffraction (Malvern Mastersizer, Malvern Instruments, Malvern, UK) was 38.3, 46.0 and 45.0 μm, respectively. The water was purified water produced by reverse osmosis (USR-Elga Ltd., High Wycombe, UK).

Table 1
Properties of the grades of microcrystalline cellulose

Sample	CMC (%)	Moisture (%)	Particle diameter[a] (μm)	Colloidal content (%)	Contact angle (°)[b]
Avicel PH101	0	<5.0	53.2	0	42.4(1.77)
Based on Avicel PH grade wet cake					
A 6	5.8	2.7	64.5	10.5	
A 8	7.8	3.5	53.8	22.4	
A 10	9.7	4.0	61.3	32.9	
A 12	11.3	4.5	55.6	34.6	
Based on Avicel RC grade wet cake					
B 6	6.0	3.6	68.2	11.1	48.8(2.12)
B 8	8.6	3.6	56.9	20.4	54.8(1.97)
B 10	10.5	3.5	61.8	33.5	
B 12	11.6	3.5	54.0	36.9	

[a] Volume mean diameter.
[b] Mean and standard deviation of five values.

2.2. Methods

2.2.1. Preparation of wet powder masses

The powders were mixed in the ratio of 20 parts of the microcrystalline cellulose and 80 parts by weight of the drug for 5 min in a planetary mixer (Hobart, Model A200, Hobart, London, UK). The appropriate quantity of water was slowly added, and the system mixed for a further 10 min, with intermittent scraping down of the side of the bowl. In some instances, the wet mass was used within 2 h of preparation, while in others the sample was placed in an airtight container and stored for 24 h before use.

2.2.2. Extrusion

The process of extrusion consists of forcing a mass of material from a large diameter through a small diameter. For pharmaceutical materials, this can be achieved in various ways, as described by Newton (2002). The extrudate produced when pastes are extruded are very dependent on the conditions of the extrusion process, as is described by Benbow and Bridgwater (1993). The best way to control these conditions as described by these workers is with a ram extruder. This system was used here to study the displacement of water during the extrusion process and to produce extrudate for spheronization. In all cases, approximately 100 g of the wet powder mass was packed by hand into a 2.54 cm diameter barrel fitted with a die of known length, 6 and 1 mm diameter. The wet mass was extruded by the application of a piston attached to the crosshead of a mechanical testing instrument (MX50, Lloyds Instruments, Southampton, UK), which travelled at known rates (50, 100, 200 and 400 mm/min). A computer recorded the force–displacement profile and the output was printed out on a *XY* recorder (Recorderlab, Gould, Surrey, UK). The measurements were carried out in triplicate when used for determination of the water displacement and as a producer of extrudate for spheronization. For water displacement measurements, extrudate was collected in previously weighed beakers for each 10 mm of piston travel. The beakers were weighed and the contents dried to constant weight at 105 °C in a fan assisted hot air oven (Pickstone Instruments, Romford, UK). For the preparation of pellets, steady state extrusion force was identified from the force/displacement curve, the sample extruded was collected from repeated runs such that at least 1 kg of extrudate was produced. The extrudate was stored in sealed moisture impermeable containers until required for use.

2.2.3. Preparation of pellets

Approximately 200 g of extrudate was placed on the 22.5 cm radial cut plate of a spheronizer (GB Caleva, Sturminster Newton, Dorset, UK) and spheronised for 10 min at 1000 rpm. The pellets were collected and dried in a hot air oven at 50 °C for 12 h.

2.2.4. Characterisation of the pellets

The size and size distribution of the pellets produced was determined by agitation for 10 min with a sieve shaker (Endecots, London, UK) fitted with a $\sqrt{2}$ progression of British Standard sieves (Endecots). From the weight retained on each sieve, a cumulative weight undersize graph was plotted from which the median diameter and the interquartile range (IQR) were determined. The pellet shape of 46 pellets from those in the modal fraction of each set of pellets (selected with a spinning riffler (Microsal Ltd., London, UK) was determined as the value of the one plane critical stability (OPCS) by the method described by Chapman et al. (1988). They showed that this method of shape assessment was more sensitive than other methods, such as aspect ratio, often used to assess pellet roundness. The good performance of the use of OPCS was confirmed by the work of Eriksson et al. (1997), who compared several methods of assessing the roundness of pellets. The mean value of the OPCS was always found to have a coefficient of variation of less than 5%.

2.2.5. Pressure membrane measurements

The pressure membrane technique described by Richards (1941) was used to determine the percentage water saturation of samples of microcrystalline cellulose as a function of applied pressure and the variation of the mean hydraulic radius of the samples as a function of pressure. Full details of the apparatus and procedures are given in Fielden et al. (1992). The calculation of the mean hydraulic radii required the value of the contact angle between water and the powder. This was deter-

mined on a compacted plate sample (10 mm × 10 mm × 2 mm) of selected cellulose samples with a Dynamic Contact Angle Analyser (DCA-312, Cahn Instruments Inc., Cerritos, California, USA). The values are the mean of five determinations for Avicel PH101 and the experimental types of MCC, B 6 and B 8.

3. Results and discussion

3.1. Screening of samples prepared with added sodium carboxymethycellulose

Details of the two series of special MCC types tested are given in Table 1. This provides materials prepared from two different wet cake systems, those from PH101, series A and those from RC 591 series B, containing different quantities of sodium carboxymethylcellulose (SCMC), 7LF grade. The test system chosen was a mixture of 20% of MCC test material with 80% lactose. It had been shown that it was possible to produce pellets from such a system if the MCC was the PH101 grade (Podczeck and Knight, 2006). Preliminary tests established two levels of water (21.8 and 23.6% of the wet weight) which appeared to offer the ability to prepare pellets. As is the usual case, below this level, the pellets were elongated rather than round. Above this level, the pellets tended to agglomerate to give larger pellets. To examine the influence of extrusion speed, ram speeds of 50 and 200 mm/min were selected as these could have an effect on the water mobility in the systems, a factor shown to be important in formulations with this level of lactose (Podczeck and Knight, 2006).

The performance of the different types of MCC was assessed in terms of (a) the ability to extrude and provide a smooth extrudate at reasonably consistent ram pressure, (b) the median weight diameter of the pellets, (c) the interquartile range of the pellet diameter and (d) the roundness of the pellets, as judged by the value of the OPCS. The results are for the two sets of types of MCC; 'A' based on the Avicel PH wet cake and 'B', based on the Avicel RC wet cake. The results in Figs. 1a and 2a show that the mixtures can be extruded at reasonable ram pressures. Very low pressures can indicate that the wet mass is too soft and will not chop into pellet length segments, while high pressures can indicate that the extrudate may not chop or if it does, will not round on the spheronizer plate. There is the expected influence of increase in ram force with increase in ram speed and decrease in water content. Both the new types of MCC appear to be less sensitive to ram speed than the standard PH101 grade of Avicel. All the systems produced extrudate, which was free from surface defects and the steady state force showed no gross fluctuation in value over the range of travel. The values of the median diameter were more consistent for the samples based on the RC wet cake (cf. Figs. 1b and 2b). The values of the IQR were low for

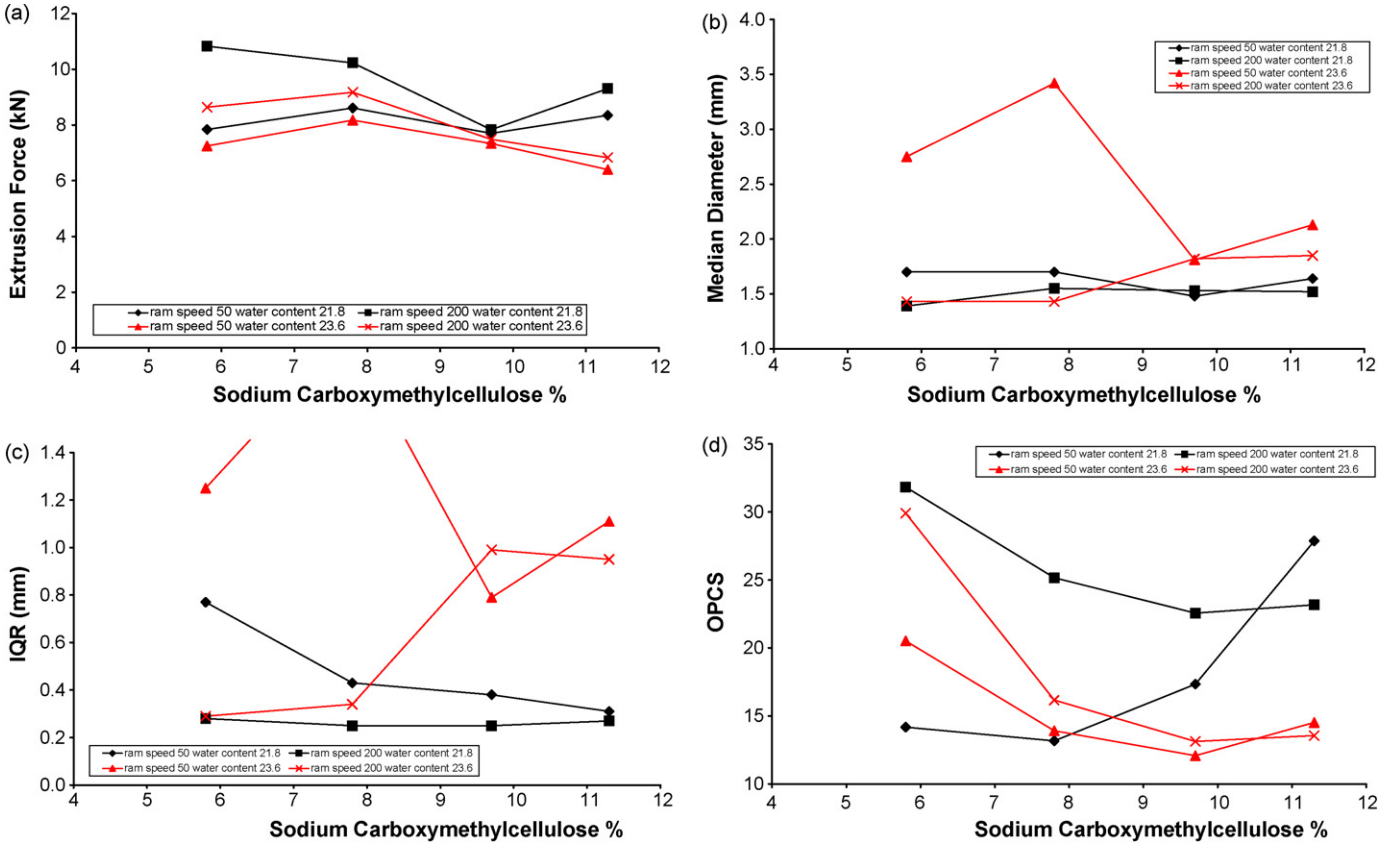

Fig. 1. The extrusion force and properties of pellets prepared with 20% of the experimental types of MCC based on the wet cake of the PH grades of MCC containing different levels of sodium carboxymethylcellulose mixed with 80% of lactose and either 21.8 or 23.6% water content. (a) Steady state extrusion pressure required to form the extrudate at ram speeds of either 50 or 200 mm/min (b) median diameter of the pellets: (c) IQR of the pellets and (d) the OPCS of the pellets. The values associated with the symbols on the figures are the ram speed and the water content of the mixture respectively.

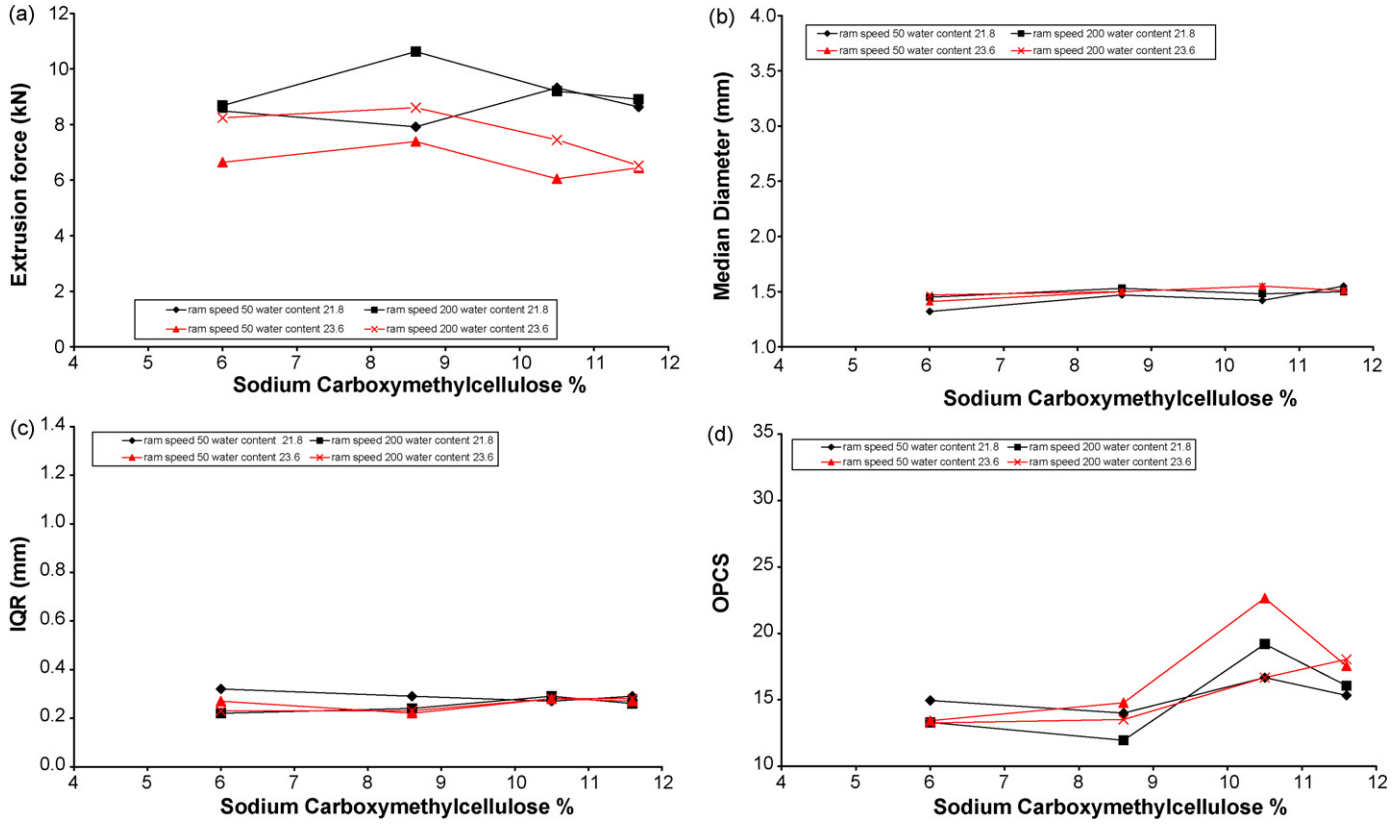

Fig. 2. The properties of pellets prepared with 20% of the experimental types of MCC based on the wet cake of the RC grades of MCC containing different levels of sodium carboxymethyl cellulose mixed with 80% of lactose and either 21.8 or 23.6% water content. (a) Steady state extrusion force used to produce the extrudate at ram speeds of either 50 or 200 mm/min through a 1 mm diameter and 6 mm length die: (b) median pellet diameter; (c) IQR and (d) OPCS. The values associated with the symbols are the ram speed and water content respectively.

the sample made from the Avicel RC wet cake but there was a far greater pellet size range obtained for samples based on the Avicel PH wet cake (cf. Figs. 1c and 2c.). This suggests that the new types are less sensitive to extrusion speed than the standard grade. An important difference between the two sets of samples lies in the ability to produce round pellets, as expressed by the values of the OPCS (cf. Figs. 1d and 2d). The series based on the RC grade wet cake (B sample), have the more consistent values for OPCS, at different water contents and extrusion speeds. When this is coupled with the consistent values for the median diameter (Fig. 2b) and the IQR (Fig. 2c), then the series B was chosen for further evaluation. As the values for OPCS are lower for the lower levels of sodium carboxymethylcellulose, those containing 6.8 and 8.6% sodium carboxymethylcellulose will be used in the rest of the study and designated the code ‘B 6’ and ‘B 8’.

3.2. Water retention by samples of MCC

The pressure membrane approach to water retention and reabsorption used by Fielden et al. (1992) allows the assessment of how the application of pressure to a MCC system completely saturated with water results in the removal of water, as the pressure is applied (drying phase), followed by assessment of the uptake of water back into the system (wetting phase), as the pressure is released. The relationship between the applied pressure and the degree of saturation of the samples is shown in Fig. 3. The levels of water saturation achieved with the experimental types of MCC are clearly higher than those attained with the standard grade, the higher level of sodium carboxymethylcellulose (B 8) providing the highest levels by some margin. In conjunction with the values for the contact angle, these curves can be used to evaluate the mean hydraulic radii of the systems as a function of the degree of saturation, as is described by Fielden et al. (1992). The results are presented in Fig. 4.

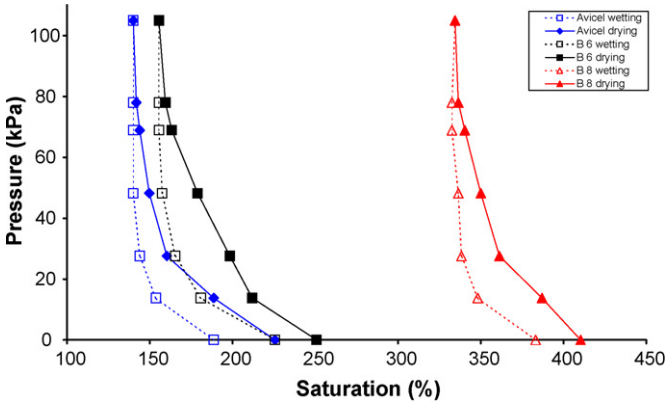

Fig. 3. The saturation pressure curve for the removal (drying, d) and uptake (wetting, w) of water from Avicel PH101, B 6 and B 8 types of MCC determined with a pressure membrane technique.

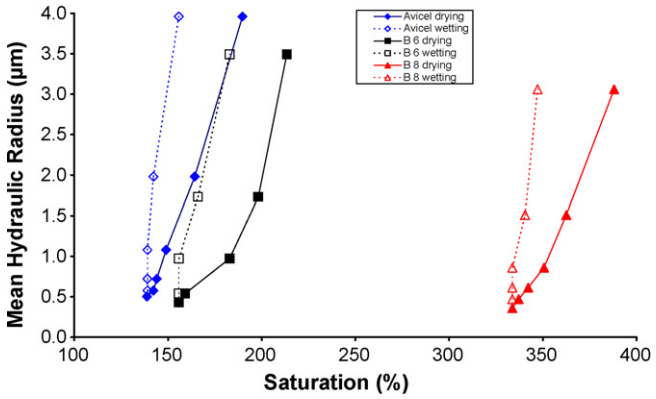

Fig. 4. The mean hydraulic radii of Avicel PH101, B 6 and B 8 types of MCC as a function of water saturation, determined with a pressure membrane technique.

The range of values for the mean hydraulic radii is similar for the different cellulose samples, but they occur at different levels of saturation. This suggests that the distance between the particles is similar but different levels of water are contained within the particles. The way cellulose holds water is known to be complex (e.g. see Li et al., 1992) and it is clear that the addition of sodium carboxymethylcellulose adds to this complexity. It would appear however, that the new types of MCC have the potential to hold greater quantities of water and limit water migration during the extrusion and spheronization processes.

3.3. Water migration during extrusion

This was assessed by the method of collecting fractions of extrudate as it emerges form the die as a function of time, using different ram speeds, as described previously (Baert et al., 1992; Tomer and Newton, 1999). The three model drugs used in the previous study with Avicel PH101 (Podczeck and Knight, 2006) have been tested at water levels for which it was found possible to form pellets. As is to be expected, these water levels will differ due to the solubility of the model drugs (Lustig-Gustafsson et al., 1999). The results for Avicel PH101 were presented in a previous paper (Podczeck and Knight, 2006) but they are represented here on a scale, which will be used for all the MCC grades tested. Results, which show this level of water migration, would appear to have the potential to function as spheronization aid. It has been chosen to incorporate the systems that formed pellets previously, i.e. there was some water migration at low extrusion speeds but when extruded at the speed used in pellet formation (200 mm/min), the systems containing either ascorbic acid or lactose formed pellets. The formulations of ibuprofen and Avicel PH101, which did not form pellets, had water migration, which was in excess of the current scale (Fig. 5a) and

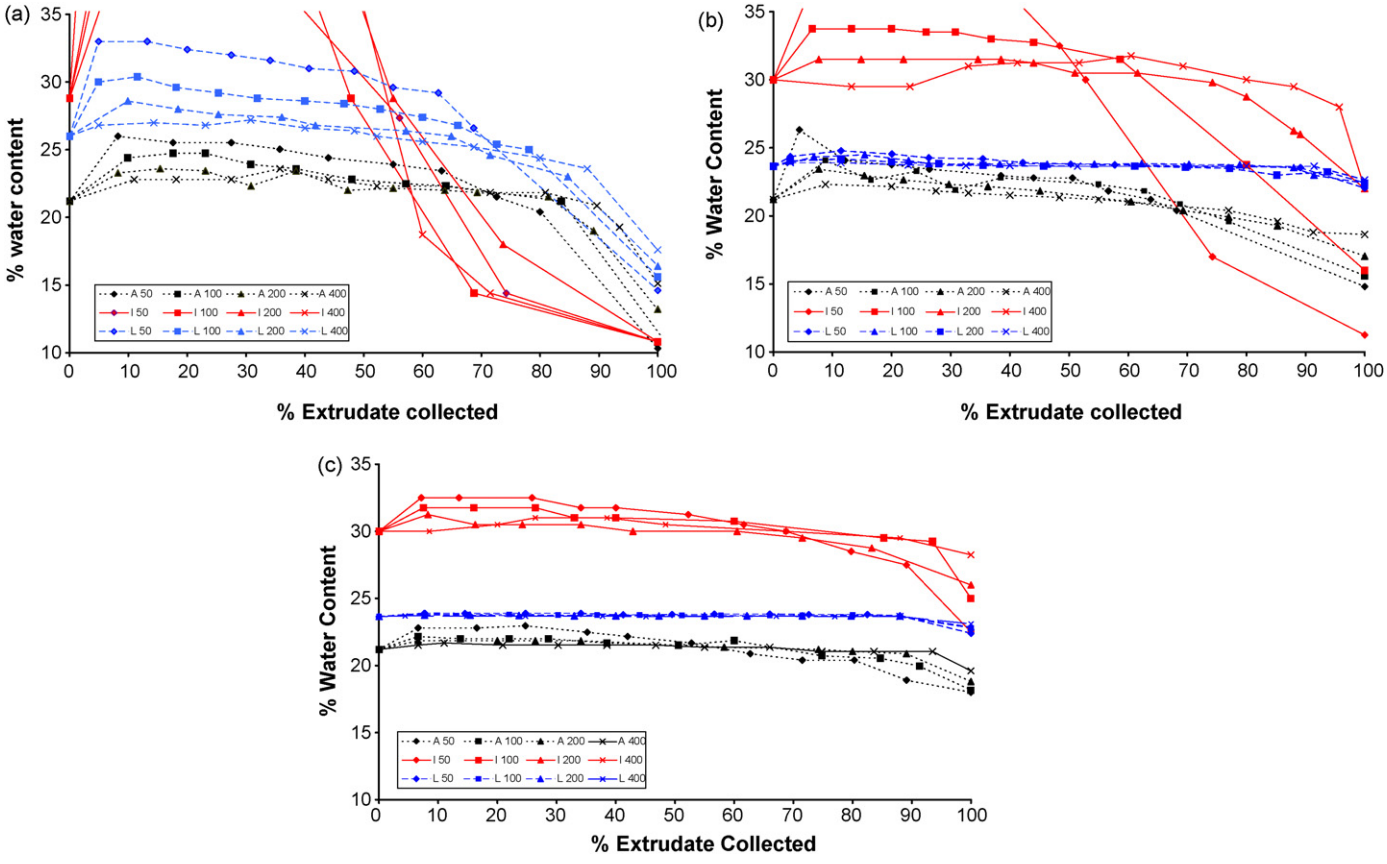

Fig. 5. The water content of the extrudate as a function of the amount of wet mass extruded at ram speeds of 50, 100, 200 and 400 mm/min extruded through a die 1 mm in diameter and 6 mm long for 80% ascorbic acid (A), ibuprofen (I) or lactose (L) mixed with 20% of (a) Avicel PH101; (b) modified MCC type B 6 or (c) modified MCC type B 8 and water. The values associated with the symbols are the ram speed for each of the model drugs.

was identified as the source of the failure of such systems to form pellets (Podczeck and Knight, 2006). The results for the B 6 and B 8 samples of MCC are shown in Fig. 5b and c and clearly show the improvement in restricting the migration of water introduced by the addition of sodium carboxymethylcellulose into the MCC. This is presumably due to the increase in the ability of these systems to hold water demonstrated by the pressure membrane technique. There is still some water migration at the lower extrusion speeds with the ibuprofen systems, but this was the system that did not function with Avicel PH101. If the mixture is extruded at 200 mm/min, the extent of migration is within the range that allowed successful pellet production with ascorbic acid and lactose mixed with Avicel PH101. The greatest restriction of water migration is with the addition of lactose, see Fig. 5c, where there is virtually no change in the water content of the extrudate at any of the extrusion speeds.

While there is a clear benefit in limiting the extent of water migration by the new types of MCC, this may not in itself ensure that pellets can be produced successfully. Tomer et al. (2001b) observed that Avicel 955 was less able to retain water in a centrifugation test than RC 591. The literature information clearly shows that the Avicel 955 grade performs better in the preparation of spherical pellets than Avicel RC 591.

3.4. Preparation of pellets

Mixtures were prepared from 80% of each of the model drugs and 20% of each of Avicel PH101, and the two experimental types of MCC, i.e. B 6 and B 8. The level of water differed for the three model drugs, as is to be expected in view of their differences in water solubility. The level of water required could differ for each of the samples of MCC, but here in the first instance, a constant level associated with a given drug was tested. Thus the levels used were 21.66, 23.66 and 29.57% respectively, for ascorbic acid, lactose and ibuprofen. These were the levels that had been used in the water migration studies. Form the values of the solubility of the model drugs (taken from the Merck Index, XIIth Edition), at these water levels one would expect about 9.0% of the lactose and 11.0% of the ascorbic acid and virtually none of the ibuprofen to dissolve in the water used in the formulation.

The results for the properties of extrusion force, median pellet diameter, the interquartile range and the OPCS for the three model drugs with the three grades of MCC are given in Table 2. It is clear that the addition of sodium carboxymethylcellulose has made it possible to form pellets from all the systems. Thus the ability to form pellets with ascorbic acid and lactose has not been lost and at this water level, in fact the new materials produced better pellets with lactose than those with Avicel PH101. A very positive addition was the ability to form pellets containing 80% ibuprofen. The pellets produced with the new materials had a median diameter, which was consistent with expectations (the modal fraction was 1.0–1.4 mm), a narrow size distribution and a shape, which is round (values of OPCS below 15.0 can be considered to be 'round' (Chapman et al., 1988).

Because it is a batch process, an important feature of the process of extrusion/spheronization is that there should be limited contamination of the plate by the wet mass. If this occurs, then the interaction between the wet mass and the plate can change and with it the effectiveness of the process of spheronization. This could require frequent cleaning of the plate, reducing the efficiency of the process. Such contamination of the plate is a characteristic of 'sticky' formulations often associated with the addition of polymers to the formulation (Erkoboni et al., 1998). To assess if this was a factor in the case of the current systems, the plate was examined after each test run, by one observer (SRC) who graded the appearance of the plate on a scale of 0–4, with 0 being completely free of contamination and 4 classifying the formulation as 'extremely sticky'. The results in Table 2 show that only the formulation of ascorbic acid and Avicel PH101 was completely free of contamination. Formulations containing MCC type B 8 were 'slightly sticky' when mixed with ascorbic acid or ibuprofen, while MCC grade B 6 was classified as 'sticky' with all three model drugs. This could have an influence on the choice of the material used in a formulation.

3.5. The influence of the amount of water

The quantity of water added to a formulation has been known for some time to be an important aspect of the formation of pellets by extrusion/spheronization, e.g. Fielden et al. (1989), Bains et al. (1991). The range of water contents which will allow pel-

Table 2
Properties of pellets produced with 80% model drug and 20% microcrystalline cellulose (MCC) from extrudate by extrusion though 1 mm diameter die 6 mm in length at 200 mm/min and spheronization for 10 min at 1000 rpm

Model drug	MCC grade	Water content (%)	Extrusion force (kN)	Median diameter (mm)	IQR (mm)	OPCS (°)	Stickiness[a]
Ascorbic acid	PH101	21.66	7.19	1.39	0.35	12.31	0
	B 6		7.67	1.27	0.24	13.11	2
	B 8		8.78	1.25	0.29	12.62	1
Ibuprofen	PH101	29.57	2.78	No pellets			
	B 6		10.81	1.22	0.28	14.61	2
	B 8		6.96	1.25	0.35	13.86	1
Lactose	PH101	23.66	5.89	1.94	0.51	17.49	2
	B 6		8.24	1.32	0.36	13.33	2
	B 8		8.61	1.45	0.36	14.00	2

[a] Scale: 0, non-sticky; 1, slightly sticky; 2, sticky; 3, highly sticky; 4, extremely sticky.

lets to be prepared is an important issue and formulations aim to provide systems that show the lowest possible sensitivity to the water content. This is particularly a problem with formulations with low levels of MCC (Bains et al., 1991; MacRitchie, 1993). To test the sensitivity of the new types of MCC, the performance of the type B 6 was compared with Avicel PH101 when the model drug was lactose. The results for the median diameter, the interquartile range and the OPCS, as a function of water content, for formulations with the experimental grade B 6 (20%) and lactose (80%) extruded at ram speeds of 50, 100 and 200 mm/min, are compared with the results for Avicel PH101 (20%), lactose (80%) formulations extruded with the same length/radius ratio die at 200 mm/min, the results being taken from MacRitchie (1993). Also included are the results from the current study for the same Avicel PH101/lactose ratio formulation at water content of 25.37%.

Pellets could be produced with a wider range of water content with the experimental B 6 type than with the Avicel PH101, Fig. 6a. The latter ceased to extrude below 21% water and even at 23% the pellets show the tendency to increase in diameter. This can occur with 'dry' formulations, where there can be a variation in the water content of the extrudate, which can lead to agglomeration. The type B 6 shows a tendency to produce larger pellets as the water level reaches 26%, especially if the wet mass is extruded at the lowest speed. This is due to the occurrence of water migration during extrusion, which will result in extrudate of variable water content, the wetter sections being the focus for agglomeration. The results for the IQR, Fig. 6b, show the same effect, increasing as the water content increases, especially at the low extrusion rates. The variation in the value of OPCS shows a consistent level over a wider range of water content for both the type B 6 and PH101 grade of MCC but the actual levels do not correspond (Fig. 6c). The B 6 type of MCC seems to function better at lower water levels, the pellets remaining round down to about 21%, whereas pellets cannot be made at all at this water level with Avicel PH101. Taking all three parameters together, the B 6 type of MCC has a better performance over a wider range of water levels than Avicel PH101 formulations.

3.6. The effect of time of storage of the wet mass prior to extrusion

As mentioned previously, the interaction between water and MCC is complex. Fielden (1987) and Raines (1990) noted that to be able to achieve reproducible values for the steady state extrusion force, it was necessary to store the MCC in contact with water for at least 12 h. With Avicel PH101 formulations, there did not appear to be an issue with the ability to make pellets provided the correct water level is identified. To test whether there was a storage effect on the MCC types B 6 and B 8, mixtures

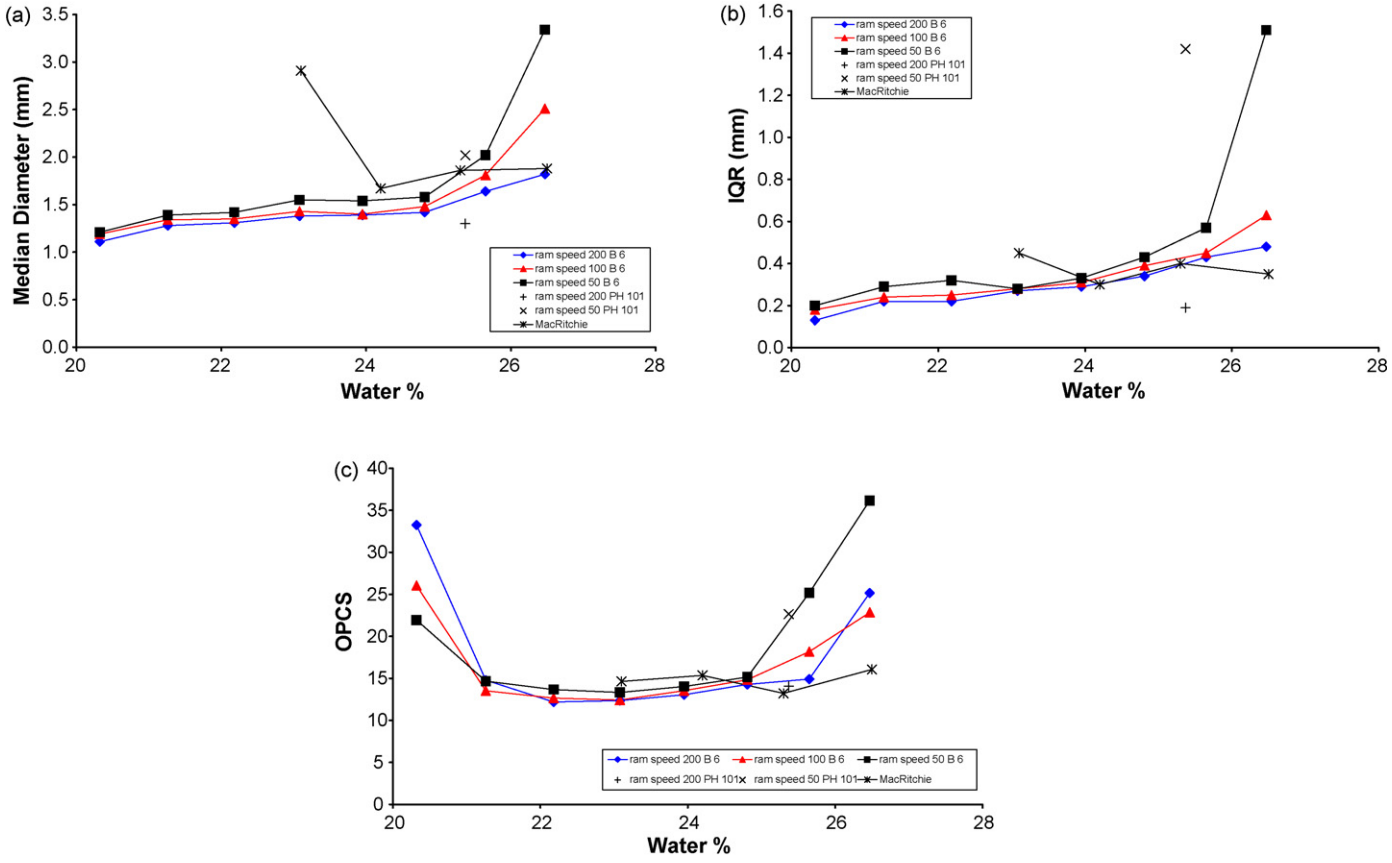

Fig. 6. Properties of pellets produced from mixtures of 80% lactose and 20% modified MCC type B 6 or Avicel (values taken from MacRitchie, 1993), as a function of water content, prepared from extrudates produced at ram speeds of 50, 100 and 200 mm/min. (a) Pellet median diameter, (b) IQR and (c) OPCS. The values associated with the symbols are for the ram speed.

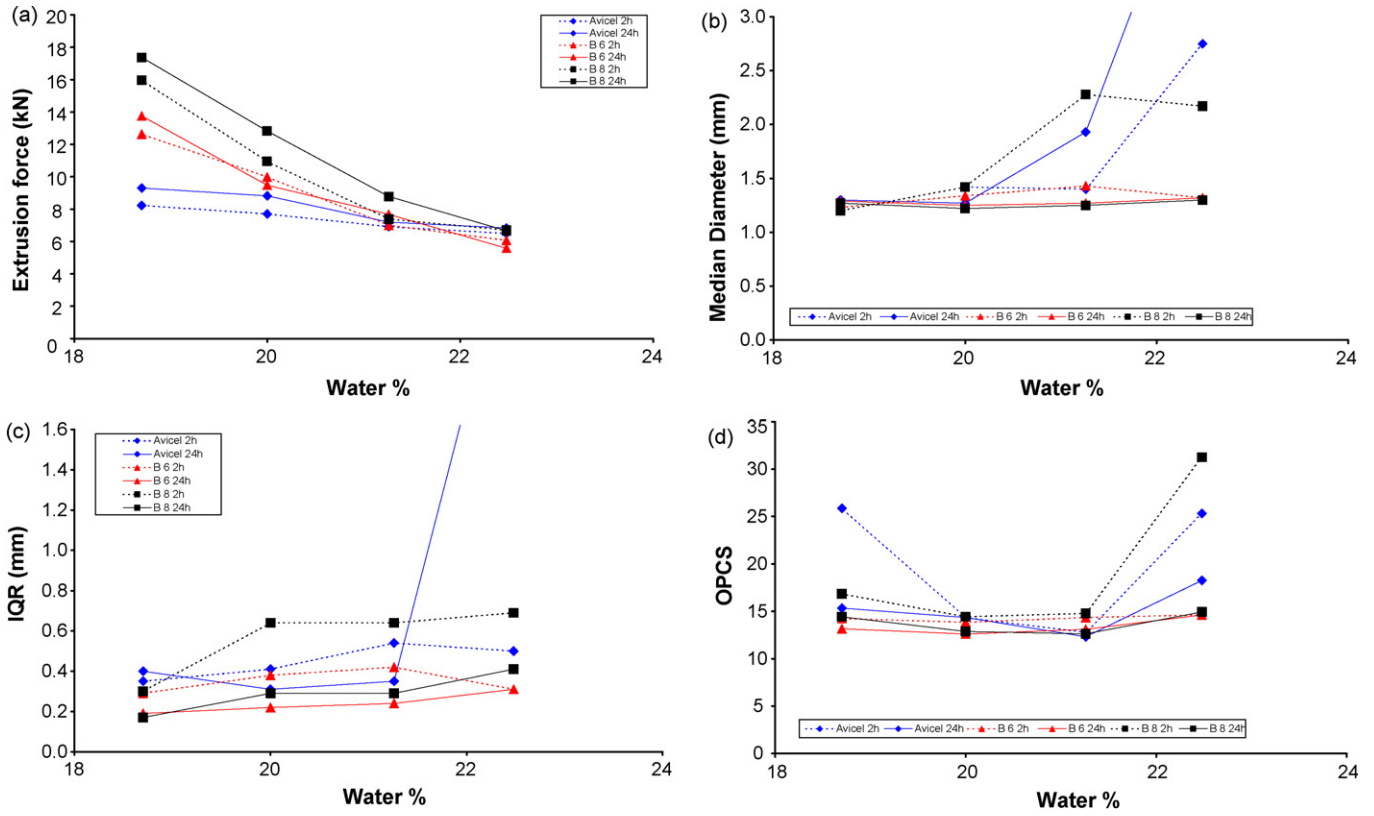

Fig. 7. Properties of pellets produced from mixtures of 20% Avicel PH101, types B 6 or B 8 modified MCC, 80% ascorbic acid and water. The wet mass was extruded within 2 h of preparation or after 24 h storage through a die 1 mm in diameter and 6 mm in length at a ram speed of 200 mm/min. (a) Steady state extrusion force, (b) pellet median diameter, (c) IQR and (d) OPCS. The values associated with the symbols are for the storage time prior to extrusion.

containing 80% of ascorbic acid and 20% of either of the two grades were mixed with three levels of water, and were extruded through 6 mm dies at 200 mm/min, either within 2 h of preparation, or after 24 h storage in a sealed container. Samples in which the experimental grades were replaced with Avicel PH101 were used as a control.

The results for the steady state extrusion force as a function of water content shows that in all cases the force increases after storage for 24 h, Fig. 7a, the effect being less for the B 6 type of MCC and at higher water levels. The 24-h storage provides the most consistent value for the value of the median diameter with the two experimental types, Fig. 7b. This differs with the Avicel PH101 grade, where for the two higher levels of water, the longer storage shows a considerable increase in the median diameter. There appears to be a change in the way the water is held in the sample, due to slow hydration of the system. The values for the interquartile range match the trends of the median diameter see Fig. 7c. In terms of roundness, there does appear to be a distinct advantage in storing the sample prior to extrusion, as the equivalent stored sample generally has a lower value for the OPCS (Fig. 7d). The greatest difference between the values of OPCS due to storage occurs with the highest water level and the B 8 types of MCC. The B 8 system stored for at least 24 h is considerably smaller in diameter (Fig. 7b) and has a lower value for the IQR (Fig. 7c). These differences are not however, related to the ability to extrude the wet mass (Fig. 7a) so there must be a more complex reason than this simple factor.

4. Conclusions

The addition of sodium carboxymethylcellulose (7LF grade) to the wet cake used to manufacture MCC produces a product that could be of potential benefit in preparing pellets containing high drug loading. Pellets prepared containing 80% of three model drugs with a range of solubility from highly soluble to low solubility were possible for systems to which 6–8% sodium carboxymethylcellulose had been added prior to spray drying the wet cake used to make Avicel RC 591. They retained the ability of Avicel PH101 to prepare satisfactory pellets from the two water soluble model drugs and provided a formulation for the water insoluble drug for which Avicel PH101 would not function. The ability of the new types of modified MCC to function as a formulation aid for the extrusion/spheronization process was found to be related to their ability to hold water when subjected to pressure. The two new types would appear to improve their performance if the wet mixture is allowed to stand for 24 h prior to being extruded. Consideration must be given to ensuring that the degree of sticking to the spheronizer plate during processing does not become excessive.

Acknowledgements

The authors wish to acknowledge FMC for the preparation of the samples and the grant to support Dr. Paul Knight in this study.

References

Baert, L., Remon, J.P., Knight, P., Newton, J.M., 1992. A comparison between the extrusion forces and sphere quality of gravity feed extruder and a ram extruder. Int. J. Pharm. 86, 178–192.

Bains, D., Boutle, S.L., Newton, J.M., 1991. The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrystalline cellulose. Int. J. Pharm. 69, 233–237.

Battista, O.A., 1971. Microcrystalline cellulose. In: Bilkales, N.M., Segal, L. (Eds.), Cellulose and Cellulose Derivatives. John Wiley and Sons, New York, USA, pp. 1265–1276.

Benbow, J., Bridgwater, J., 1993. Paste Flow and Extrusion. Clarendon Press, Oxford, UK.

Chapman, S.R., Newton, J.M., Rowe, R.C., 1988. Characterisation of the sphericity of particles by the one plane critical stability. J. Pharm. Pharmacol. 40, 503–505.

Chatchawalsaisin, J., Podczeck, F., Newton, J.M., 2005. The preparation by extrusion/spheronization and the properties of pellets containing drugs, microcrystalline cellulose and glyceryl monostearate. Eur. J. Pharm. Sci. 24, 35–48.

Chopra, R.A., Podczeck, F., Newton, J.M., Alderborn, G., 2002. The influence of pellet shape and film coating on the filling of pellets into hard shell capsules. Eur. J. Pharm. Biopharm. 53, 327–333.

Chohan, R.K., Newton, J.M., 1996. Analysis of extrusion of some wet powder masses used in extrusion/spheronization. Int. J. Pharm. 131, 210–217.

Cox, E.P., 1927. A method of assigning numerical and percentage values to the degree of roundness. J. Paleont. 1, 179–183.

Eriksson, M., Alderborn, G., Nyström, C., Podczeck, F., Newton, J.M., 1997. Comparison between and evaluation of some methods for the assessment of the sphericity of pellets. Int. J. Pharm. 148, 149–154.

Erkoboni, D.F., Fiore, S.A., Wheatley, T.H., 1998. Microcrystalline cellulose spheronization composition. United States Patent 5,725,886.

Fielden, K.E., 1987. Extrusion and spheronization of microcrystalline cellulose and lactose mixtures. Ph.D. Thesis, University of London, UK.

Fielden, K.E., Newton, J.M., Rowe, R.C., 1992. Movement of liquids through powder beds. Int. J. Pharm. 79, 47–60.

Fielden, K.E., Newton, J.M., Rowe, R.C., 1989. The effect of lactose particle size on the extrusion properties of microcrystalline cellulose. J. Pharm. Pharmacol. 41, 217–221.

Hileman, G.A., Goskonda, S.R., Spalitto, A.J., Upadrashta, S.M., 1993a. A factorial approach to high dose product development by an extrusion/spheronization process. Drug Dev. Ind. Pharm. 19, 483–491.

Hileman, G.A., Goskonda, S.R., Spalitto, A.J., Upadrashta, S.M., 1993b. Response surface optimization of high dose pellets by extrusion and spheronization. Int. J. Pharm. 100, 71–79.

Jalal, I.M., Malinowska, H.J., Smith, W.E., 1972. Tablet granules composed of spherical-shaped particles. J. Pharm. Sci. 61, 1466–1467.

Jover, I., Podczeck, F., Newton, J.M., 1996. Evaluation by a statistically designed experiment, of an experimental grade of microcrystalline cellulose, Avicel 955, as a technology to aid the production of pellets with high drug load. J. Pharm. Sci. 85, 700–705.

Li, T.-Q., Henricksson, O., Klasen, T., Odberg, L., 1992. Water diffusion in wood pulp cellulose fibres studied by means of the pulse spin-echo method. J. Colloid Interface Sci. 154, 305–315.

Lustig-Gustafsson, C., Kaur Johal, H., Podczeck, F., Newton, J.M., 1999. The influence of water content and drug solubility on the formulation of pellets by extrusion/spheronization. Eur. J. Pharm. Sci. 8, 147–152.

MacRitchie, K.A., 1993. Rheological evaluation of mixtures of lactose, microcrystalline cellulose and water suitable for the preparation of spherical granules. Ph.D. Thesis, University of London, UK.

MacRitchie, K.A., Newton, J.M., Rowe, R.C., 2002. The evaluation of the rheological properties of lactose/microcrystalline cellulose and water mixtures by controlled stress rheometry and the relationship to the production of spherical pellets by extrusion/spheronization. Eur. J. Pharm. Sci. 17, 42–50.

Malinowski, H.J., Smith, W.E., 1975. The use of factorial design to evaluate granulations prepared by spheronization. J. Pharm. Sci. 64, 1688–1692.

Newton, J.M., 2002. Extrusion and extruders. In: Swarbrick, J., Boylan, J.C. (Eds.), Encyclopaedia Pharmaceutical Technology, vol. 2, second ed. Marcell Dekker Inc., New York, USA, pp. 1220–1236.

Newton, J.M., Chow, A.K., Jeewa, K.B., 1992. The effect of excipient source on spherical granules made by extrusion/spheronization. Pharm Tech. Int. 4 (8), 52–58.

O'Connor, R.E., Schwartz, J.B., 1984. Spheronization. II: Drug release from drug-diluent mixtures. Drug Dev. Ind. Pharm. 11, 1837–1857.

Podczeck, F., Knight, P., 2006. The evaluation of formulations for the preparation of pellets with high drug loading by extrusion/spheronization. Pharm. Dev. Technol. 11, 263–274.

Raines, C.L., 1990. The extrusion of various formulations of microcrystalline cellulose. Ph.D. Thesis, University of London, UK.

Raines, C.L., Newton, J.M., Rowe, R.C., 1990. Extrusion of microcrystalline cellulose formulations. In: Carter, R.E. (Ed.), Rheology of Food, Pharmaceuticals and Biological Materials with General Rheology. Elsevier Applied Science, London, UK, pp. 248–257.

Reynolds, A.D., 1970. New technique for the production of spherical particles. Manuf. Chem. Aerosol News 41 (6), 40–44.

Richards, L.A., 1941. A pressure-membrane extraction apparatus for silo suction. Soil Sci. 51, 277–386.

Tomer, G., Newton, J.M., 1999. Water movement evaluation during extrusion of wet powder masses by collecting extrudate fractions. Int. J. Pharm. 182, 71–77.

Tomer, G., Podczeck, F., Newton, J.M., 2001a. The influence of type and quantity of model drug on the extrusion/spheronization of mixtures with microcrystalline cellulose. I: Extrusion parameters. Int. J. Pharm. 217, 237–248.

Tomer, G., Patel, H., Podczeck, F., Newton, J.M., 2001b. Measuring the water retention capacities (MRC) of different microcrystalline cellulose grades. Eur. J. Pharm Sci. 12, 321–325.

Tomer, G., Podczeck, F., Newton, J.M., 2002. The influence of model drugs on the preparation of pellets by extrusion/spheronization. II: Spheronization parameters. Int. J. Pharm. 231, 107–119.

Yuen, K.H., Deshmukh, A.A., Newton, J.M., 1993. Development and in vitro evaluation of a multiparticulate sustained release theophylline formulation. Drug Dev. Ind. Pharm. 19, 855–874.