ELSEVIER

International Journal of Pharmaceutics 230 (2001) 25–33

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Pharmaceutical applications of size reduced grades of surfactant co-processed microcrystalline cellulose

S.R. Levis, P.B. Deasy *

Department of Pharmaceutics and Pharmaceutical Technology, School of Pharmacy, Trinity College, University of Dublin, Dublin 2, Ireland

Received 20 February 2001; received in revised form 9 July 2001; accepted 31 July 2001

Abstract

New grades of ultra-fine microcrystalline cellulose (MCC), without (grade X) or with variable percentage sodium lauryl sulphate (SLS; grades Y), were prepared by an ultrasonic homogenisation process from Avicel® PH-101 (grade C), prior to recovery by spray-drying. Both new grade types were found to be inferior compared with grade C in a tableting application for paracetamol, resulting largely from poor flow of the feed material. However, both new grades proved superior to grade C in an aqueous extrusion/spheronisation application for the preparation of indomethacin pellets, producing smoother pellets in greater yield. Grade Y was particularly effective at delaying drug dissolution, due mainly to decreased porosity in the pellets formed and retardation of their break-up. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Ultra-fine grades; Paracetamol tablets; Indomethacin pellets; Spheronisation aid

1. Introduction

Two new grades of size-reduced (~ 15 μm) microcrystalline cellulose (MCC), denoted as grade X, or grade Y if co-processed with 1% sodium lauryl sulphate (SLS), have been prepared conveniently by ultrasonic homogenisation of an aqueous slurry of coarser commercial MCC (~ 50 μm, Avicel® PH-101, FMC, grade C), followed by recovery as dry powder by spray-drying. Details of their preparation and extensive characterisation have been published (Levis and Deasy, 2001), which suggest that they may have unique functionality for pharmaceutical formulation. We have reported previously (Deasy and Law, 1997) that MCC treated by physically mixing with SLS surprisingly delayed drug release from pellets containing indomethacin prepared by extrusion–spheronisation.

This paper examines the use of these new grades, compared with grade C and another appropriate commercial grade of MCC, in a range

* Corresponding author. Tel.: + 353-1-608-2784; fax: + 353-1-608-2783.

E-mail address: pdeasy@tcd.ie (P.B. Deasy).

PII: S0378-5173(01)00843-2

of model formulations for tablet and pellet production. These studies will help identity whether the new grades have beneficial formulation properties in the production of dosage forms for which currently available commercial grades of MCC are employed. The advantages and disadvantages of the new grades of sized reduced MCC will be related to their physicochemical properties.

2. Materials and methods

2.1. Materials

Cetrimide, sodium citrate, sodium hexametaphosphate (Aldrich), citric acid monohydrate, di-sodium hydrogen phosphate dodecahydrate, sodium hydroxide (Riedel de Haen), granular paracetamol (Rhone Poulenc), indomethacin (20 μm, Ind. Chimica Farmaceutica), lactose α-monohydrate (Granulac 200 mesh, Meggle), MCC (Avicel® PH-101, grade C and PH-102, grade D), polysorbate 20 (Tween 20), SLS (Sigma), stearic acid (Merck) and glass distilled water were used.

2.2. Preparation of size reduced grades of MCC

Avicel® PH-101, with or without added SLS (0.3125 or 0.625%, grades Y1 and Y2, respectively, used in extrusion/spheronisation application; 1%, grade Y used in tableting application) to an aqueous 5% suspension, was size reduced by multiple passes through an ultrasonic homogeniser (Minisonic, Ultrasonics Ltd.). Size reduced material was recovered as a powder by spray-drying (Buchi 190) the continuously agitated slurry, using optimised settings of delivery rate at 5–10 ml/min, air flow rate at 600 NI h and inlet temperature at 125 °C.

2.3. Particle size analysis by laser diffraction

Particle sizes of the various grades of MCC were examined by dry-powder or powder-in-liquid techniques using a laser diffraction particle analyser (Malvern 2600c), with a 300 mm lens attached, which is capable of measuring particles in the size range 5.8–564 μm.

2.4. Tableting procedures and formation of MCC compacts

Powder mixes containing 100 g of 55.1% granular paracetamol, 44.7% with each of the four grades of MCC and 0.2% stearic acid as lubricant were blended together in a cube mixer (Erweka) at 40 rpm for 15 min. A single station tablet press (model 1B 179, Manesty) fitted with a 12.5 mm flat-faced punch and die set was used to compress 550 mg of mix containing Avicel® PH-101 to an average breaking stress of 10 kPa approximately. The same tablet press settings were used for the compression of mixes containing the other grades of MCC and the tablet output was 60 per min.

Compacts of the various grades of MCC (400 mg compression weight) were prepared using an IR press with a flat-faced 13 mm punch and die set (Perkin–Elmer) at 1000, 2000, 3000, 4000 or 5000 kg of compression force for 1 min. The average tensile strength (σ) of compacts was determined using the following equation:

$$\sigma = \frac{2P}{\pi DE}$$

where P is the average tablet hardness (kg/cm^2), D the average compact diameter (cm) and E is the average compact thickness (cm) as measured using an optical micrometer (Graticules Ltd.).

2.5. Tablet evaluation

Tablet testing was performed in accordance with European Pharmacopoeia (EP) requirements. Uniformity of weight and content were determined on samples of 20 tablets from each batch. Hardness measurements on samples of ten tablets were performed using a hardness tester (model 6D, Schleuniger Pharmaton). The crushing strength of tablets of varying thickness was compared by calculating their tensile strength as described previously (El-Mahdi and Deasy, 2000). Friability of samples of 20 tablets was determined using a friabilator (model TA 20, Copley). Disintegration testing on samples of six tablets was performed using suitable equipment (model ZT 44, Copley). Uniformity of drug content was based on the assay of a sample of 20 powdered

tablets equivalent to 150 mg paracetamol, whose drug content was extracted into 200 ml 0.025 M NaOH solution, filtered and after appropriate dilution with dilute NaOH solution was ultraviolet (UV) assayed at λ_{max} of 257 nm.

2.6. Preparation of pellets

Dry powders were mixed for 10 min in a planetary mixer (Kenwood) and then wetted by gradual addition of the required volume of water. After being stored for 12–24 h in a sealed container to ensure uniform hydration of the mix, the wetted mass was extruded through a 1 mm diameter screen using a gravity fed cylinder extruder (Alexanderwerk GA 65). The extrudate formed was spheronised on a Caleva 120 mini spheroniser fitted with a cross-hatch cut stainless-steel friction plate. The spheronised pellets were dried in a forced circulation oven (type UL40, Memmert) for at least 48 h at 40 °C.

2.7. Sieve analysis and yield of pellets

Sieve analysis on either the whole batch or on random samples obtained by a splitting technique was performed using a nest of standard sieves, 1680, 1180, 850 and 300 μm, agitated for 10 min on a sieve shaker (Endecott) and the retained weight data obtained was used to construct a frequency distribution. The desired size of pellets was in the range 850–1180 μm and is referred subsequently to as 'pellets'. Those which occurred above this size range are referred to as 'large pellets', while those below are referred to as 'fines'.

2.8. Dissolution testing of tablets and pellets

Each of six paracetamol tablets was subject to dissolution testing at 37 °C for 6 h in 1 l of McIlvaine's buffer pH 6.8 using a paddle rotating at 100 rpm, located 25 mm above the base of the vessel (Copley DT6). Samples (5 ml) were withdrawn periodically with immediate replacement of the dissolution medium, and following filtration through a 0.45 μm filter (Gelman), were assayed by UV spectroscopy (Shimadzu UV-160) at 257 nm.

Samples of pellets containing indomethacin were agitated at 100 rpm in 1 l pH 6.8 medium at 37 °C in an EP dissolution basket assembly (Erweka DT6), where adequate sink conditions existed. Filtered withdrawn samples were assayed at 318 nm.

Similarity factors (f_2) for comparing dissolution profiles were calculated and interpreted as described by Tang and Gan (1998).

2.9. Hexane intrusion and mercury porosimetry studies on pellets

The apparent density of pellets at 25 °C was determined using a density bottle and hexane, which was a non-solvent for the components of the pellets. The intra-particle porosity (ε) of the pellets was computed as follows (Kleinebudde, 1994):

$$\varepsilon(\%) = \left(\frac{1-\rho_g}{\rho}\right)100$$

where ρ_g is the apparent density of the pellets and ρ is the true density of the materials.

Mercury porosimetry was performed using a PoreSizer 9320 system (Micromeritics). Measurements were performed on pellet samples using a 3 cm^3 'powder sample' penetrometer (sample weight 350 mg). Samples were dried to constant weight using a vacuum oven set at 80 °C and removed just prior to analysis. Intrusion pressures between 0.5 and 30 000 psi were used, corresponding to pore diameters between 360 and 0.006 μm. The low pressure analysis (0.5 to $\sim$20 psi) was done semiautomatically and the high pressure analysis was automatically controlled, both using the equilibrium mode with a time interval of 10 s.

2.10. Scanning electron microscopy (SEM) studies on pellets

Samples from batches of pellets were mounted on aluminium stubs using double-sided sticky tape, vacuum coated with gold film (Polaron SC 500) and examined using a scanning electron microscope (LEO Stereoscan S-360) for surface morphology.

Table 1
Uniformity of weight of paracetamol tablets produced using different grades of MCC

Grade	Average (g)	S.D. (g)	CV (%)
C (Avicel® PH-101)	0.5543	0.0122	2.20
D (Avicel® PH-102)	0.5470	0.0107	1.96
X (~15 μm MCC)	0.4993	0.0441	8.83
Y (~15 μm MCC+SLS)	0.5331	0.0317	5.95

S.D., standard deviation; CV, coefficient of variation.

2.11. Carr's index and Hausner ratio determinations for pellets

The packing density of pellets was determined by pouring pre-weighed samples of pellets into a 100 ml graduated cylinder and the 'poured volume' noted. The 'tapped volume' was determined after manually dropping the cylinder from a height of 2 cm onto a hard surface 500 times at 2-s intervals. From the calculated poured density (ρ_{min}) and tapped density (ρ_{max}), Carr's index $[(\rho_{max} - \rho_{min})/\rho_{max}]100\%$ and Hausner ratio ρ_{max}/ρ_{min} were determined as indirect indices of ease of pellet flow (Carr, 1965; Hausner, 1967).

3. Results and discussion

3.1. Tableting application

The uniformity of weight of paracetamol tablets produced from feed material differing only in the grade of MCC used and employing identical tablet press settings is shown in Table 1. Both commercial grades of MCC (Avicel® PH-101 and PH-102) promoted the formation of very uniformly weighted tablets. The slightly lower average weight of the Avicel® PH-102 containing tablets is due to its larger porosity associated with its greater particle size, causing lower bulk density and hence comparable volumes of feed which result in tablets with reduced weights.

The two new grades of MCC promoted the formation of lighter and less uniformly weighted tablets. This is related to the poor flow properties of fine grades of MCC, as has been reported by Patel and Reier (1994). Coarser Avicel® PH-102 was introduced by FMC to help overcome poor flow properties in certain tablet mixes observed with PH-101. SLS in the new grade Y appears to enhance the flowability of the feed, compared with its absence in grade X, by forming a coating on the MCC particles as reported previously (Levis and Deasy, 2001), reducing surface irregularity and static effects within the powder bed.

The hardness and friability of samples of paracetamol tablets prepared using the four grades of MCC are shown in Table 2, indicating that in this tableting application the two new grades produced the weakest tablets. This is probably due to incomplete and variable die filling caused by the poorer flow properties of these grades, which comprise almost half of the compression weight. It is possible that the process of producing the finer grades of MCC reduced its compactibility by increasing intra-particle hydrogen bonding, the effect termed 'quasi-hornification' by Staniforth and Chatrath (1996). Undesirable sticking problems during compression were observed also with

Table 2
Hardness and friability of paracetamol tablets produced using different grades of MCC

Grade	Hardness		Friability	
	Average (kPa)	S.D.	Average (%)	S.D.
C (Avicel® PH-101)	10.61	1.26	0.87	0.19
D (Avicel® PH-102)	11.29	1.56	0.79	0.11
X (~15 μm MCC)	7.67	3.89	1.08	0.21
Y (~15 μm MCC+SLS)	8.68	2.86	0.90	0.34

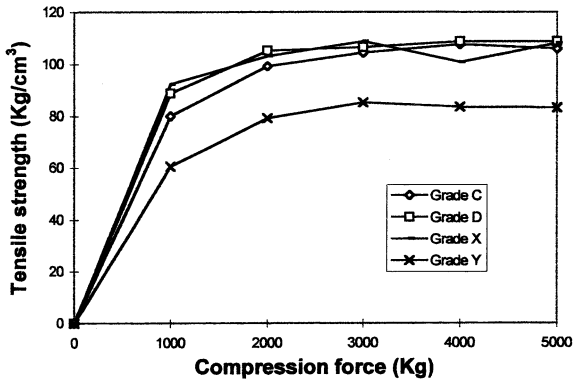

Fig. 1. Tensile strength of compacts of different grades of MCC as a function of compression force (mean of six determinations).

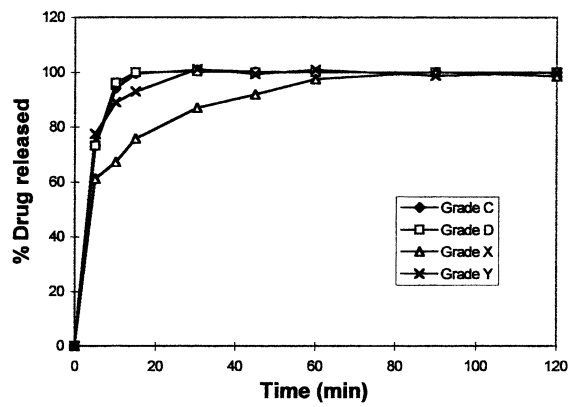

Fig. 2. Dissolution profiles of paracetamol tablets prepared using different grades of MCC in McIlvaine buffer pH 6.8 at 37 °C.

the new grades, as their finer powder tended to seep down into the gap between the die and lower punch walls, hindering free movement of the latter.

Fig. 1 shows the results of tensile testing on compacts formed under different loads and containing only different grades of MCC. It is evident that the tensile strength of all compacts increased rapidly at low compression force, irrespective of the grade of MCC used, indicating capacity to make hard tablets at relatively low compaction pressure, where disintegration should not be over impeded. A maximum tensile strength was achieved with increasing compression force, the lowest such value being obtained with grade Y, which because of its coating by SLS of the MCC particles involved, reduced inter-particulate bonding.

The disintegration time of the paracetamol tablets prepared using the four grades of MCC discussed above was very rapid, being less than 1 min in all cases, with a tendency for the new experimental grades to delay disintegration slightly. Likewise all the batches of tablets complied with the current EP uniformity of content test.

The results of dissolution testing on the four batches of tablets are shown in Fig. 2. The tablets prepared with the new size reduced grades had slower release profiles over the first hour of testing, presumably related to the reduced porosity of the finer matrix produced, compared with the two commercial grades that had almost identical release profiles. The faster drug release from tablets prepared using grade Y, compared with grade X, is probably related to the presence of SLS in the former aiding wetting of the drug.

Collectively the results of this study suggest that the two new size reduced grades of MCC are inferior in most aspects to existing commercial grades promoted for use in tablets. This is related to their very fine particle size, which hinders flow leading to formation of tablets with difficulty, and having more variable weight and disintegration time. The only aspect shown in this tableting application where the new grades may have an advantage over existing grades is in the design of sustained release dosage forms, and because paracetamol is not a suitable candidate drug for such an application, this aspect is examined in more detail by forming a pelletised product of indomethacin as discussed in the next section.

3.2. Extrusion–spheronisation application

Avicel® PH-101 is the most widely used aid for aqueous extrusion spheronisation in the production of drug loaded spherical pellets. It is capable of retaining large amounts of the water added to the mix, facilitating lubrication and plasticity during processing, aiding binding in the dried spheres. As product yield and quality are influ-

enced by the level of water added, preliminary experiments were performed to help optimise this variable, prior to detailed examination of the new size reduced MCC (grade X) and with two different levels of added SLS, compared with Avicel PH-101 (grade C) as control (all grades 30%), in a typical extrusion spheronisation application involving indomethacin (30%), with lactose (40%) added as filler. Lower levels of SLS were employed in the initial slurry than in the tableting application in an attempt to better replicate conditions of the experimental work on physical mixes reported by Deasy and Law (1997). Fig. 3

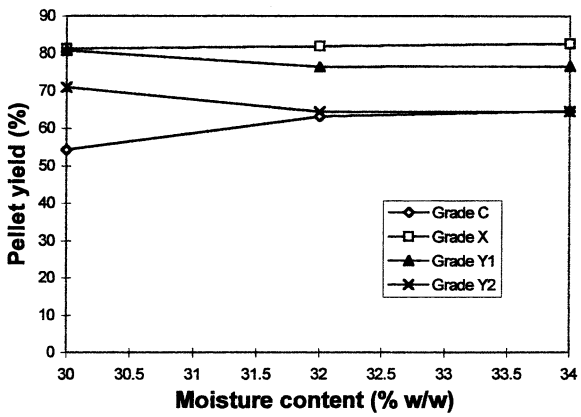

Fig. 3. Plot of the effect of water content on the yield of pellets, keeping spheronisation time and speed constant at 10 min and 1250 rpm, respectively.

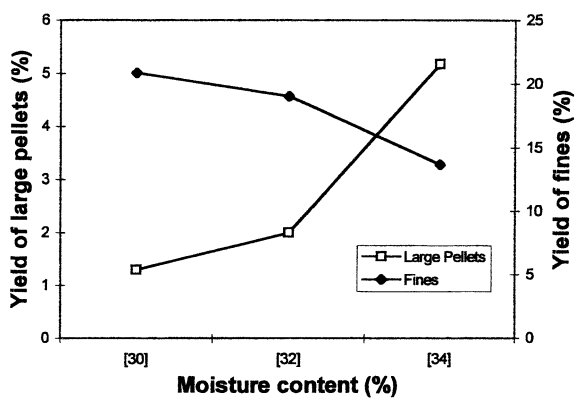

Fig. 4. Effect of water content added on the yield of large pellets and fines prepared by extrusion/spheronisation of an indomethacin formulation containing grade Y2 MCC.

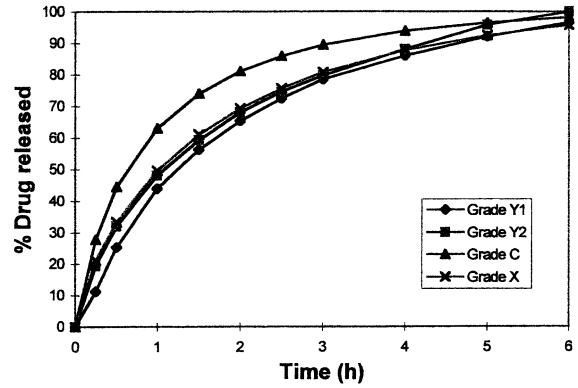

Fig. 5. Dissolution of indomethacin from pellets in McIlvaine buffer pH 6.8 for 6 h at 37 °C.

Table 3
Similarity factors (f_2) comparing the dissolution profiles of indomethacin (i) drug only with that from pellet formulations containing the indicated grade of MCC or (ii) the control grade C with the new novel grades

(i) Drug only versus	(ii) Control pellets versus
Grade X 21.5	Grade X 51.1
Grade Y1 18.8	Grade Y1 42.7
Grade Y2 19.8	Grade Y2 49.9
Grade C 27.0	

shows the effect of added water level in the optimal range on the yield of pellets recovered after drying. Most formulations under optimum conditions of hydration were capable of producing pellets with yields in excess of 80%. The poorest yields were obtained with Avicel® PH-101, indicating that all the novel grades employed resulted in an improvement in pellet yield relative to the control, presumably related to their finer particle size ($\sim$ 15 μm). Fielden et al. (1992) investigated the effect of different grades of lactose in formulations consisting of MCC and either coarse (118 μm) or fine grade (18 μm) lactose on their ability to spheronise and on their sensitivity to moisture content. Their results indicated that the pellets produced using the finer grade were less sensitive to moisture content. The results from this study illustrate similar behaviour for MCC in that the novel size reduced grades appear less sensitive to moisture level added, compared with the coarser

control. The formulation containing the higher level of SLS co-processed with the MCC (grade Y2), like the control, was particularly sensitive to water level added as illustrated in Fig. 4, where increasing water content appears to favour formation of large pellets and decreased yield of fines.

Fig. 5 shows the dissolution profiles for drug release from the pellets formed using the various grades of MCC. The dissolution profiles for the pellet formulations indicate that all showed retardation in drug release relative to the powdered drug (100% dissolution within 1 h). This was confirmed by calculating similarity factors (f_2) as listed in Table 3, comparing the dissolution profile of the pure drug with each of the pellet formulations. In all cases the value of f_2 was less than 50, whereas an f_2 value between 50 and 100 suggests that the compared dissolution profiles are similar. Table 3 also shows the similarity factors comparing the release profile of pellets formed using grade C with those using the novel grades of MCC, confirming a significant retardation in drug release for grade X and also the grades incorporating SLS, which is unexpected as SLS is a wetting agent expected to aid penetration of dissolution medium into pellets. However, the retarded release is in agreement with the results reported by Deasy and Law (1997). The release profile obtained with grade X was not significantly different from grades Y1 and Y2, the sight differences apparent particularly between grade X and grade Y2 being due probably to the SLS aiding smaller pore formation and densification.

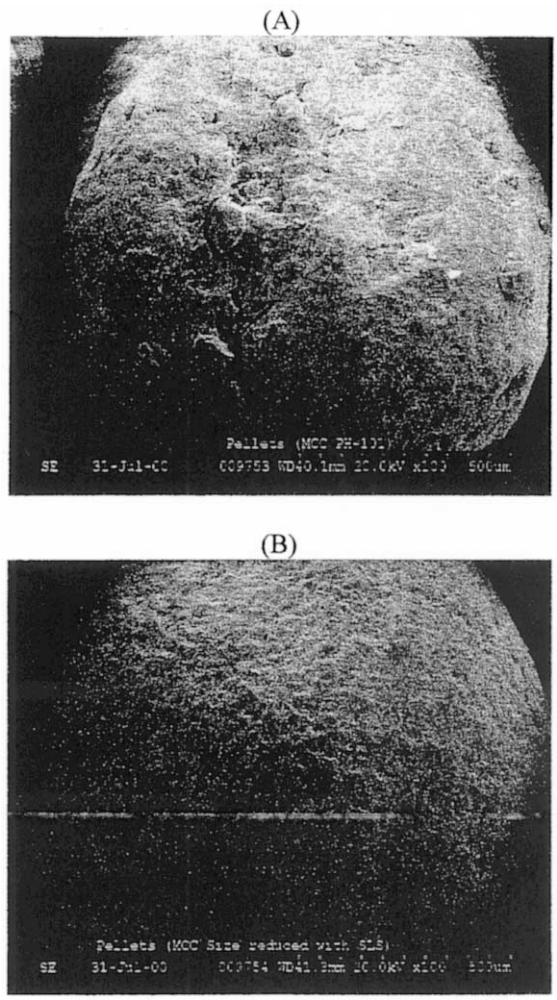

Fig. 6. Scanning electron micrographs of pellets prepared using grade C (A) or grade Y2 (B) MCC.

When two other commonly employed de-aggregating agents, sodium citrate and sodium hexametaphosphate (6.25 and 12.5%), were examined as co-processed grades with MCC (93.75 and 87.5%), they did not cause significant reduction in drug release relative to the control grade C, indicating that the phenomenon was specific to the use of SLS. Likewise preliminary experiments with indomethacin loaded pellets prepared with physical mixes of two other surfactants, cetrimide or polysorbate 20 (5 and 10% of the MCC content), failed to demonstrate any retarded drug release, compared with control pellets prepared with Avicel® PH-101 and lactose without surfactant. In fact faster drug release was detected with these examples of cationic and non-ionic surfactants, which was ascribed on visual examination to much more rapid break-up of these surfactant containing pellets, compared with the control. The SLS containing pellets like the control tended to remain intact for a longer duration of dissolution testing in McIlvaine buffer pH 6.8 at 37 °C for 6 h.

In an attempt to gain insight into the mechanism whereby SLS retards drug release from the drug loaded pellets, the intra-particulate porosity was calculated from knowledge of the true density

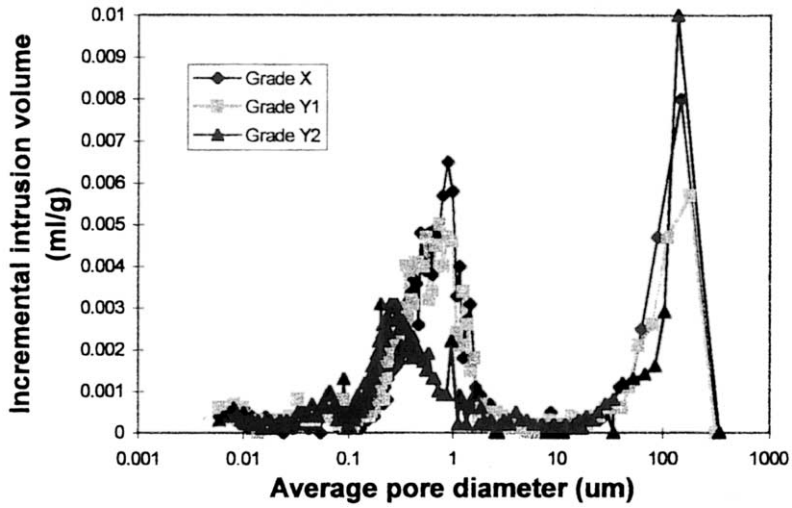

Fig. 7. Incremental mercury intrusion plots for pellets containing various grades of MCC.

of the materials and the pellet density. The pellets, which had the lowest porosity values were those prepared using SLS containing grades Y1 and Y2. This low porosity may be responsible for their observed delayed drug release by hindering the penetration of dissolution medium into the pellet matrix and hence slowing the rate of drug dissolution and release. However, the hexane intrusion technique used is based on passive solvent diffusion and will not intrude into smaller pores for which a high-pressure technique is required.

Therefore, the porous characteristics of the pellets were studied also using high-pressure mercury porosimetry, which gives a more accurate determination of overall intra-particulate porosity. Average values of 18.9 and 17.8% were obtained for pellets prepared with grades Y1 and Y2, respectively, with values of 17.9 and 59.4% obtained using grades X and C, respectively, confirming that the coarser control MCC grade favoured the formation of much more porous pellets. The larger particle size of the MCC used to produce the control pellets containing Avicel PH-101, together with their greater porosity, results in a coarser pellet surface and less rounder product relative to pellets incorporating the novel finer grades, as is illustrated in Fig. 6, showing scanning electron micrographs of two representative samples.

The incremental intrusion plots for the pellet formulations incorporating the novel grades of MCC are shown in Fig. 7, the plots showing a bimodal distribution of pore sizes. Coarse pores are evident in the size range 5–500 μm. This is due to gaps present between individual pellets when they are packed together and also is an indicator of the smoothness of the pellet surfaces. The maximum intrusion of mercury in this range is 0.01 and ~0.2 ml/g for pellets prepared using novel and Avicel® PH-101 grades of MCC, respectively, confirming the much rougher surfaces

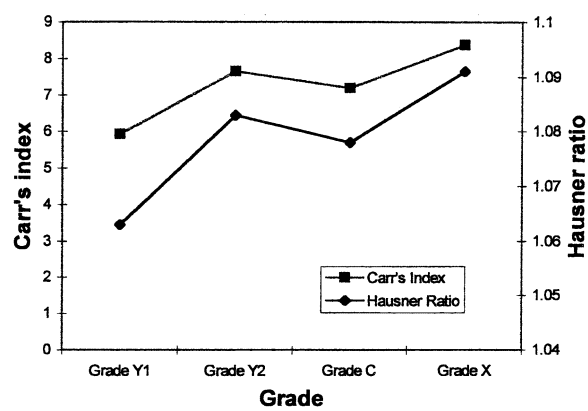

Fig. 8. Carr's indices and Hausner ratios for pellet formulations produced under optimum moisture content and with various grades of MCC.

of the latter. Fine pores in the range 0.1–1.2 μm for pellets containing the novel grades of MCC can be interpreted as intra-particulate. The corresponding pores in the control pellets range from 10 to 20 μm (not shown in Fig. 7 to aid clarity), facilitating greater ease of penetration of dissolution medium into these pellets and explaining their faster drug release. The inference from the porosimetry results in relation to pellet pore size are in agreement with the SEMs shown in Fig. 6, which show much larger pores in the control pellets.

It is evident from Fig. 8 that all pellet formulations have excellent flow properties. Both Carr's index and Hausner ratio are below the cut-off level indicative of free flowing granules, namely 15% and 1.25, respectively. Pellets containing grade Y1 MCC was the only one with improved flowability over the control, indicating that its level of SLS may contribute to this effect.

4. Conclusions

Whereas size reduced grades of MCC hindered good tablet production, with the exception of a SLS containing grade retarding drug release, these novel size reduced grades aided extrusion–spheronisation. Grade Y1 produced the greatest improvements in the procedure, with pellet yields greater than 80% at optimal hydration levels, maximum drug release retardation and improved flow properties over the control formulation incorporating Avicel® PH-101, which has long been considered the best excipient for use in aqueous extrusion–spheronisation. The drug retardant effect was observed only with the anionic surfactant, while other classes of surfactants examined promoted drug release by causing premature rupture of pellets during testing. The amount of surfactant liberated into the large excess of dissolution medium was well below its critical micelle concentration and should not have affected drug solubility by solubilisation. Adoption of our findings for SLS containing systems, with possible further optimisation, should lead to an improved commercial grade of co-processed MCC for use in this procedure.

Acknowledgements

The work was supported by a grant from FMC Corporation and Enterprise Ireland under the Irish American Partnership Programme.

References

Carr, R.L., 1965. Evaluating flow properties of solids. Chem. Eng. 72, 163–168.

Deasy, P.B., Law, M.F.L., 1997. Use of extrusion–spheronisation to develop an improved oral dosage form of indomethacin. Int. J. Pharm. 148, 201–209.

El-Mahdi, I.M., Deasy, P.B., 2000. Tableting of coated ketoprofen pellets. J. Microencap. 17, 133–144.

Fielden, K.E., Newton, J.M., Rowe, R.C., 1992. A comparison of the extrusion and spheronisation behaviour of wet powder masses processed by a ram extruder and a cylinder extruder. Int. J. Pharm. 81, 225–233.

Hausner, H.H., 1967. Friction conditions in a mass of metal powder. Int. J. Powder Metall. 3, 7–13.

Kleinebudde, P., 1994. Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: II. Swelling properties. Int. J. Pharm. 109, 221–227.

Levis, S.R., Deasy, P.B., 2001. Production and evaluation of size reduced grades of microcrystalline cellulose. Int. J. Pharm. 213, 13–24.

Patel, N.K., Reier, G.E., 1994. An evaluation of microcrystalline cellulose and lactose excipients using an instrumented single station tablet press. Int. J. Pharm. 110, 203–210.

Staniforth, J.N., Chatrath, M., 1996. Towards a new class of high functionality tablet binders. I: quasi hornification of microcrystalline cellulose and loss of functionality. Proceedings of the AAPS Conference, PT 6206.

Tang, Y., Gan, K., 1998. Statistical evaluation of in vitro dissolution of different brands of ciprofloxacin hydrochloride tablets and capsules. Drug Dev. Ind. Pharm. 24, 439–552.