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Research article

Use of hydrophilic polymers with microcrystalline cellulose to improve extrusion–spheronization

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Abstract

Microcrystalline cellulose 19 parts was combined with sodium carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose or polyvinylpyrrolidone one part, either by spray-drying or physical mixing. This combined excipient (20%) mixed with lactose (80%) and water was added to aid formation of pellets by the process of extrusion–spheronization. Spray-dry combined excipient produced pellets with higher yield, better sphericity and improved tolerance to minor variation in the level of water added, compared with the physical mix excipient. Physicochemical testing based on scanning electron microscopy with energy dispersive analysis, differential scanning calorimetry and X-ray diffraction analysis, indicated that the spray-drying with the hydrophilic polymer caused disintegration of the microcrystalline cellulose component into smaller crystallites, favouring its more uniform dispersion throughout the lactose during subsequent processing. The hydroxypropyl cellulose or polyvinylpyrrolidone containing excipients were the most satisfactory of the hydrophilic polymers examined, because they had the least adhesive strength favouring maximum yield of highly spherical pellets. © 1998 Elsevier Science B.V.

Keywords: Extrusion–spheronization; Microcrystalline cellulose; Hydrophilic polymers; Spray-drying; Physical mixing

1. Introduction

The most commonly used excipient to aid aqueous extrusion–spheronization is microcrystalline cellulose (MCC), particularly the commercial grade, Avicel® PH-101. This material when dry mixed in adequate concentration with a drug acts as a molecular sponge for the added water, usually forming a plastic mass which may extrude well prior to forming well-rounded pellets in a spheronizer. However variation of several process factors, particularly level of hydration, extruder and spheronizer speed, and residence time in the spheronizer can have a marked effect upon the yield and quality of the desired product, making the process sensitive to minor changes in such variables. Consequently successful spheronization requires extensive preliminary studies to optimize process conditions and when developed can be difficult to consistently replicate in production.

This project is concerned with the examination of a range of hydrophilic polymers as adhesive binder in association with MCC to improve the yield and sphericity of pellets formed, and to help make the process more tolerant to minor alterations in two key variables affecting the process (moisture content and spheronizer speed). The influence of the incorporation method of the hydrophilic polymer is also studied using factorially designed experiments. Lactose is used as a substitute for a drug in these developmental studies, particularly as it is the most frequently employed filler and major excipient in low-dose containing pellets manufactured by extrusion–spheronization.

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Table 1
Design of 2^3 factorial experiments

Design factor	Key	Low level (−)	High level (+)	Range of variation
Polymer/MCC	*M*	PM	SD	—
Water content (%)	*W*	25	30	5
Spheronizer speed (rpm)	*S*	1250	1750	500

Polymer/MCC is polymer/Avicel® PH-101 mix.
PM, physical mix; SD, is spray-dried.
Water was included as a percentage in addition to the total dry powder weight (100%).

2. Materials and methods

2.1. Materials

Hydroxypropyl cellulose—HPC (LF grade, Colorcon, Orpington, UK), hydroxypropylmethyl cellulose—HPMC (E50 grade, Dow, Hounslow, UK), lactose alpha monohydrate (Granulac® 200 mesh, Meggle, Wasserburg, Germany), microcrystalline cellulose—MCC (Avicel® PH-101, FMC, Cork, Ireland), nitrogen, oxygen-free (Air Products, Dublin, Ireland), polyvinylpyrrolidone—PVP (Povidone K24-26, GAF, Manchester, UK), sodium carboxymethylcellulose—NaCMC (low viscosity grade, BDH, Poole, UK) and glass-distilled water were used.

2.2. Methods

2.2.1. Preparation of spray-dried mixes

The polymer and MCC in the ratio of 1:19 were prepared as a 10% solid dispersion in water and the continuously agitated slurry was spray-dried using a mini spray-dryer (Buchi 190, Goppingen, Germany) with optimized settings of delivery rate at 5 ml/min, air flow rate at 600 NI/h and inlet temperature at 125°C.

2.2.2. Preparation of pellets

Dry powders were mixed for 10 min in a planetary mixer (Kenwood, Havant, UK) and then wetted by gradual addition of the required amount 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 screen with 1 mm diameter openings using a gravity fed cylinder extruder (Alexanderwerk GA 65, Remscheid, Germany). The extrudate formed was spheronized on a 120 mini spheronizer (Caleva, Sturminster Newton, UK) fitted with a cross-hatch cut stainless-steel friction plate. The design of the 2^3 factorial experiments is shown in Table 1.

2.2.3. Sieve analysis and yield of pellets

Sieve analysis on the whole batch of pellets was performed using a nest of standard sieves, 1680, 1180, 850 and 300 μm, agitated for 10 min on a sieve shaker (Endecotts, London, UK) and 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 subsequently referred to as 'pellets'. Those which occurred above this size range are referred to as 'large pellets', while those below are referred to as 'fines'.

Table 2
2^3 full factorial fit for pellet yield (%) using NaCMC

Estimated effects and coefficients				
Term	Effect	Coefficient	*t*-value	*P*
Constant		57.22	93.67	<0.001
M	10.30	5.15	8.43	<0.001
W	−31.29	−15.65	−25.61	<0.001
S	−6.48	−3.24	−5.31	<0.001
M * *W*	0.90	0.45	0.74	0.483
M * *S*	−2.33	−1.17	−1.91	0.093
W * *S*	6.27	3.14	5.13	<0.001
M * *W* * *S*	−2.33	−1.16	−1.91	0.093

Analysis of variance (ANOVA)					
Source of variation	df	SS	MS	*F*	*P*
Main effects	3	4509.39	1503.13	251.76	<0.001
Two-way Interactions	3	182.33	60.78	10.18	0.004
Three-way Interactions	1	21.69	21.69	3.63	0.093
Residual error	8	47.76	5.97		
Total	15	4761.17			

M, type of polymer/MCC mix; *W*, water content; *S*, spheronizer speed; df, degrees of freedom; SS, sequential sum of squares; MS, adjusted mean squares; *F*, *F*-statistic and *P*, is the *P*-value which is the probability associated with the *F*-statistic.

Table 3
2^3 full factorial fit for pellet yield (%) using HPMC

Estimated effects and coefficients					
Term	Effect	Coefficient	*t*-value	*P*	
Constant	—	53.56	119.12	<0.001	
M	7.75	3.87	8.62	<0.001	
W	−33.85	−16.93	−37.64	<0.001	
S	−17.36	−8.68	−19.31	<0.001	
M * *W*	1.95	0.97	2.17	0.062	
M * *S*	1.01	0.51	1.13	0.293	
W * *S*	0.42	0.21	0.47	0.649	
M * *W* * *S*	0.10	0.05	0.11	0.914	
Analysis of variance (ANOVA)					
Source of variation	df	SS	MS	*F*	*P*
Main effects	3	6030.04	2010.01	621.29	<0.001
Two-way Interactions	3	19.99	6.66	2.06	0.184
Three-way Interactions	1	0.04	0.04	0.01	0.914
Residual error	8	25.88	3.24	—	—
Total	15	6075.96	—	—	—

2.2.4. Image analysis of pellets

The sphericity of the pellets was determined using derived pellet parameters measured by an image analysis system (Quantimet 520, version 4.0, linked to an Ergolux microscope, Cambridge Instruments, Cambridge, UK). A random sample of 150–200 pellets from each batch of product was examined and a roundness function was calculated as follows:

$$\text{Roundness factor} = \frac{P_m^2}{4\pi A}$$

where P_m is the perimeter length and A is the projected area. A perfectly round pellet would have a value of 1.0 irrespective of size and the value would tend towards 10.0 for pellets that were progressively non-spherical. However in order to facilitate a correlation between increasing sphericity value and increasing pellet roundness, the reciprocal of the roundness factor was calculated and termed 'sphericity', where values tending toward 0.1 denote progressive lack of roundness and 1.0 indicates a perfect sphere.

2.2.5. Scanning electron microscopy and energy dispersive analysis

Samples from batches of pellets were mounted on aluminium stubs using double-sided sticky tape, vacuum coated with gold film (Polaron SC 500 sputter coater, Microtech, Uckfield, UK) and examined using a scanning electron microscope (Leo Stereoscan S-360, Leo, Cambridge, UK). For energy dispersive analysis, powder samples were carbon coated (Polaron E6300 vacuum evaporator, Microtech, Uckfield, UK) and examined with the same microscope linked to an energy dispersive X-ray analysis system (AN 10/855 with Pentefet detector, Oxford Instruments, High Wycombe, UK).

Table 4
2^3 full factorial fit for pellet yield (%) using HPC

Estimated effects and coefficients					
Term	Effect	Coefficient	*t*-value	*P*	
Constant	—	50.04	123.42	<0.001	
M	4.27	2.14	5.27	<0.001	
W	9.49	4.75	11.70	<0.001	
S	−10.84	−5.42	−13.36	<0.001	
M * *W*	0.35	0.18	0.43	0.677	
M * *S*	−0.41	−0.21	−0.51	0.625	
W * *S*	3.33	1.66	4.10	0.003	
M * *W* * *S*	1.28	0.64	1.57	0.155	
Analysis of variance (ANOVA)					
Source of variation	df	SS	MS	*F*	*P*
Main effects	3	903.06	301.02	114.44	<0.001
Two-way Interactions	3	45.39	15.13	5.75	0.021
Three-way Interactions	1	6.50	6.50	2.47	0.155
Residual error	8	21.04	2.63	—	—
Total	15	976.00	—	—	—

Table 5
2^3 full factorial fit for pellet yield (%) using PVP

Estimated effects and coefficients					
Term	Effect	Coefficient	*t*-value	*P*	
Constant	—	64.94	103.38	<0.001	
M	6.19	3.10	4.93	<0.001	
W	11.75	5.87	9.35	<0.001	
S	−16.07	−8.04	−12.79	<0.001	
M * *W*	−1.84	−0.92	−1.46	0.181	
M * *S*	−2.15	−1.07	−1.71	0.126	
W * *S*	2.54	1.27	2.02	0.078	
M * *W* * *S*	−0.15	−0.07	−0.12	0.909	
Analysis of variance (ANOVA)					
Source of variation	df	SS	MS	*F*	*P*
Main effects	3	1739.04	579.68	91.82	<0.001
Two-way Interactions	3	57.73	19.24	3.05	0.092
Three-way Interactions	1	0.09	0.09	0.01	0.909
Residual error	8	50.50	6.31	—	—
Total	15	1847.37	—	—	—

2.2.6. Differential scanning calorimetry of excipients

Powder samples of excipients (5–7.5 mg) were examined in closed aluminium pans under nitrogen purge by differential scanning calorimetry (Mettler TA3000 thermal analysis system, Gießen, Germany) using a ramp rate of 5°C/min over the range 30–350°C.

2.2.7. X-ray diffraction analysis of excipients

The X-ray diffraction measurements were made on powdered samples of excipients in conventional cavity mounts using a DACO MP wide-range goniometer (Siemens, Erlangen, Germany) with a 1.00° dispersion slit, a 1.00° antiscatter slit and a 0.15° receiving slit. The Cu anode X-ray tube was operated at 40 kV and 20 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays ($\lambda = 1.5418$ Å).

2.2.8. Statistical analysis of data

The statistical package used in the analysis of experiments was Minitab for Windows, version 10.1 (Minitab, State College, PA). All tests were conducted at 0.05 level of significance.

Table 6
Yield data for large pellets (>1180 μm) and fines (<850 μm) obtained with the inclusion of the various polymers over the experimental design

Polymer	Type of yield	Highest yield (%)	Lowest yield (%)	Range (%)
NaCMC	Large pellets	64.81	4.29	60.52
	Fines	15.09	1.02	14.07
HPMC	Large pellets	79.33	12.69	66.64
	Fines	12.29	0.64	11.65
HPC	Large pellets	49.16	29.11	20.05
	Fines	23.65	1.02	22.63
PVP	Large pellets	42.76	8.25	34.51
	Fines	19.89	6.12	13.77

3. Results and discussion

3.1. Spray-dried product and pellet yield

The yield of spray-dried material obtained when processing various polymer 5%, MCC 95% combinations as a slurry in water, using optimized spray-dryer conditions, was 45.3, 47.1, 79.4 and 86.8% for NaCMC, HPMC, HPC and PVP respectively, based on a minimum of five runs. The main loss in yield was due to adherence of product to the inner wall of the spray chamber and accordingly the reported order of increasing yield is an index of decreasing adhesive property.

A series of 2^3 factorial designed experiments were performed to examine the type of polymer/MCC mix (spray-dried or physical), water content and spheronizer speed on properties of the pellets formed. A typical dry mix contained 20% of polymer:MCC 1:19 and 80% lactose. The extruder speed and residence time were kept constant at 60 rpm and 10 min respectively. Each experiment was conducted in replicate and the order of runs was fully randomized. The yield of pellets in the desired size range 850–1180 μm using NaCMC and fitted to a full factorial model is shown in Table 2, from which it can be seen that a number of effects are significant ($P < 0.05$). The positive effect for the type of NaCMC/MCC mix indicates that an estimated 10.3% improvement in pellet yield was achieved when the spray-drying method was used. However an increase in water content over the range 25–30% was found to result in a significant reduction in pellet yield by 31.29%. An increase in spheronizer speed from 1250 to 1750 rpm was also seen to reduce pellet yield by 6.48%.

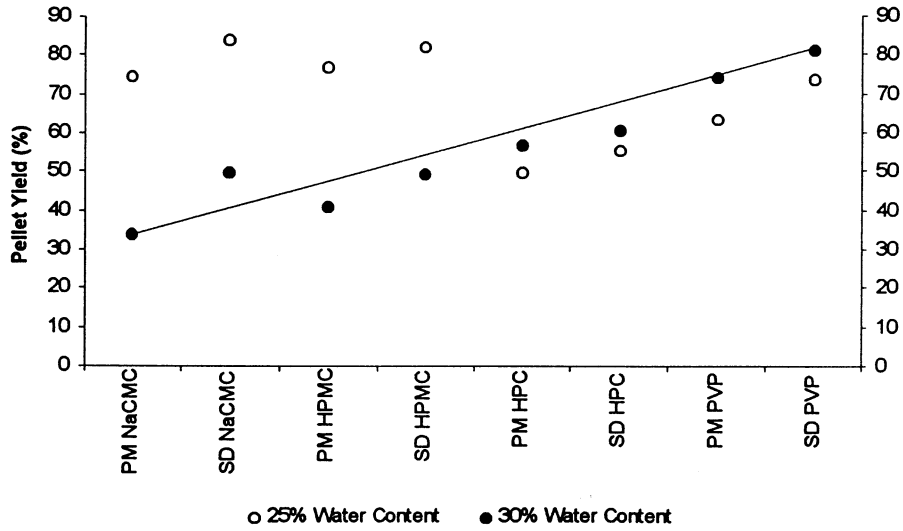


Fig. 1. Comparison of pellet yields obtained from mixes containing 80% lactose and 20% various polymer:MCC (1:19) incorporations by spray-drying (SD) or physical mixing (PM) with added 25 or 30% water, using 1250 rpm spheronizer speed.

A significant two-way interaction occurred between water content and spheronizer speed, implying that their main effects were confounded with each other.

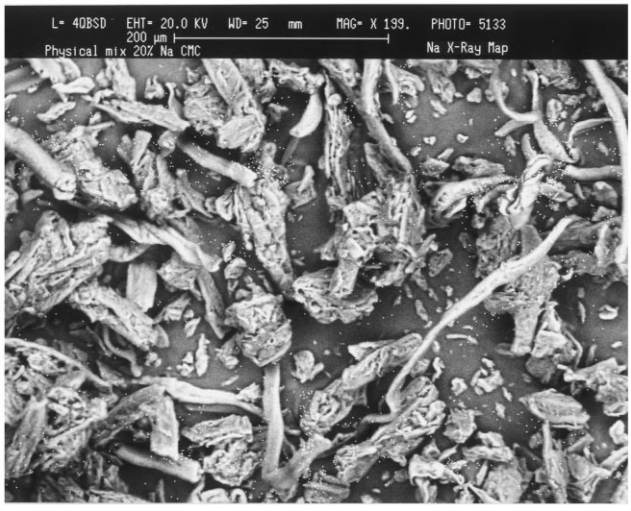
Similar factorial analysis showed that when HPMC (Table 3) or HPC (Table 4) was used with identical experimental design, the effect of using spray-dried compared with physical mixes was to significantly improve the yield of pellets by 7.75 and 4.27% respectively. Increase in water content was associated with significant decrease in yield for HPMC (33.85%) and increase in yield for HPC (9.49%). Increase in spheronizer speed reduced pellet yield with both polymers (17.36%, HPMC; 10.84%, HPC). No significant two-way and three-way interactions occurred between all three variables, except for that between water content and spheronizer speed using HPC. Likewise when PVP (Table 5) was used, significant increase in pellet yield (6.19%) was observed with the spray-dried incorporation compared with the physical mix. Increase in water content or spheronizer speed produced corresponding increase (11.75%) or decrease (16.07%) in pellet yield, and no significant multi-way interactions were observed.

Table 7
Mean yield and sphericity of pellets prepared at a spheronization speed of 1250 rpm

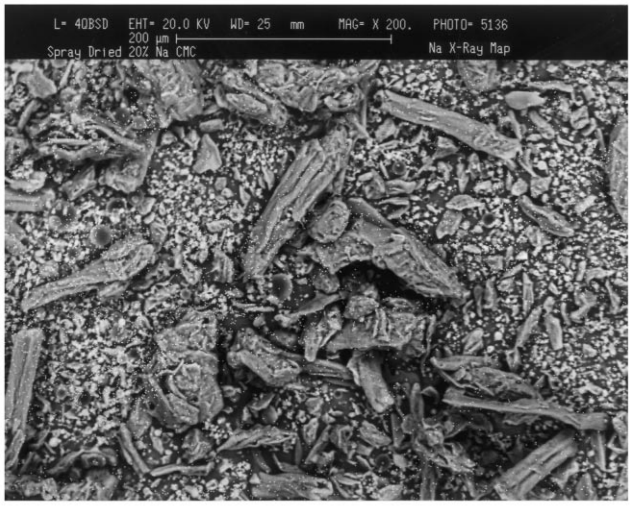
Type of polymer/ MCC mix	Water content (%)	Yield (%)	Sphericity
PM NaCMC/MCC	25	74.54	0.8051
PM NaCMC/MCC	30	33.75	0.8578
SD NaCMC/MCC	25	83.95	0.8083
SD NaCMC/MCC	30	49.62	0.8711
PM HPMC/MCC	25	76.94	0.8021
PM HPMC/MCC	30	40.82	0.8572
SD HPMC/MCC	25	81.83	0.8054
SD HPMC/MCC	30	49.40	0.8710
PM HPC/MCC	25	49.58	0.8650
PM HPC/MCC	30	56.67	0.8721
SD HPC/MCC	25	55.19	0.8692
SD HPC/MCC	30	60.43	0.8766
PM PVP/MCC	25	63.36	0.8539
PM PVP/MCC	30	74.26	0.8737
SD PVP/MCC	25	73.39	0.8629
SD PVP/MCC	30	80.91	0.8748
Control	25	84.35	0.8271
Control	30	83.88	0.8411

PM, polymer/MCC is physical mix of polymer:MCC, 1:19; SD, polymer/MCC is spray-dried polymer:MCC, 1:19.
Control is 20% MCC and 80% lactose.

The coefficients for the more adhesive polymers such as NaCMC and HPMC indicate that the level of water is more important for these polymers, with increasing levels having a negative impact on pellet yield. Thus the experimental design space may be in a more optimal place for the less adhesive polymers such as HPC and PVP, than for the more adhesive polymers. Subject to this constraint, collectively the results indicate that the incorporation of a hydrophilic polymer with MCC by spray-drying improves pellet yield compared with physical mixing, irrespective of its identity within the range examined. Detailed examination of the results showed that inclusion of the more adhesive NaCMC or HPMC polymers was associated with greater range in the yield of pellets over the experimental design irrespective of method of incorporation, indicating that the use of the less adhesive HPC or PVP polymers gave more control over the efficiency of spheronization. Data on the yield of non-ideal sized pellets as shown in Table 6, con-



(i)



(ii)

Fig. 2. Scanning electron micrographs with dot-map of sodium distribution in (i) physical mix and (ii) spray-dried mix of NaCMC:MCC, 1:4 (magnification $\times 200$).

firmed that the more adhesive polymers favoured the formation of higher large pellet yield, whereas the less adhesive polymers favoured greater production of fines. It was noted also that the more adhesive polymers required lower levels of water to spheronize successfully, as over-hydration tended to cause the wet mass to adhere to the side-wall and friction plate of the spheronizer promoting agglomeration to oversize pellets. Increasing speed tended to contribute mainly to agglomeration.

Fig. 1 shows a comparison of pellet yield for formulations containing the various polymer/MCC combinations prepared with the two levels of hydration at a spheronizer speed of 1250 rpm. The trend-line shown for pellet yield at the higher water level indicates that pellet yield increases in the order PVP > HPC > HPMC > NaCMC, supporting an inverse relationship to polymer adhesive strength. A less obvious relationship is apparent at the lower moisture content, but at both moisture levels examined the spray-dried incorporation always produced high pellet yield, compared with the physical mix.

3.2. Sphericity of pellets

The number of random samples used to obtain a single sphericity value was between 150 and 200. Higher sphericity values were obtained in comparable mixes wetted with the higher water content (30%), whose results are shown in Table 7. Pooled two sample t-tests were conducted to compare the sphericity of pellets prepared using the spray-dried and physical mix. Like the results obtained at 25% water content, within any polymer type, spray-drying incorporation always gave more spherical pellets ($P < 0.05$), with smoother surfaces. Paired difference t-tests were conducted between the sphericity values obtained for the SD and PM mixes, the results indicating that the sphericity of pellets prepared using the SD mix are significantly higher compared with the PM mix ($P < 0.05$). Table 7 also shows that inclusion of auxiliary polymer, either by physical mixing or preferably by spray-drying, produced better rounded pellets compared with a control prepared in its absence by physical mixing. Within either method of incorporation at 30% water content, the more adhesive polymers NaCMC and HPMC gave lower sphericity values, presumably by promoting surface adhesion within the bed of spheronizing pellets leading to greater surface unevenness and reduced yield as reported above.

Avicel® RC-591 and other colloidal grades were found to be unsatisfactory when used in extrusion–spheronization [1], because the materials favoured cohesion rather than plasticity, resulting in the production of mixtures of spheres and short rods. This was confirmed by Newton et al. [2], who observed that longer residence times were required to produce spheres, suggesting that mixes containing these colloidal grades required higher stresses to induce flow [3]. This effect was seen to a lesser extent from the high sphericity value (0.87), compromised however by larger median diameter and reduced pellet yield, obtained for pellets prepared using the spray-dried NaCMC/MCC containing mix with 30% added water, presumably because of the lower NaCMC content compared with the Avicel® colloidal grades. Pellets with similar large median diameter were produced by Newton et al. [2] from mixes containing Avicel® RC-501 (7.1–11.9% NaCMC content, bulk-

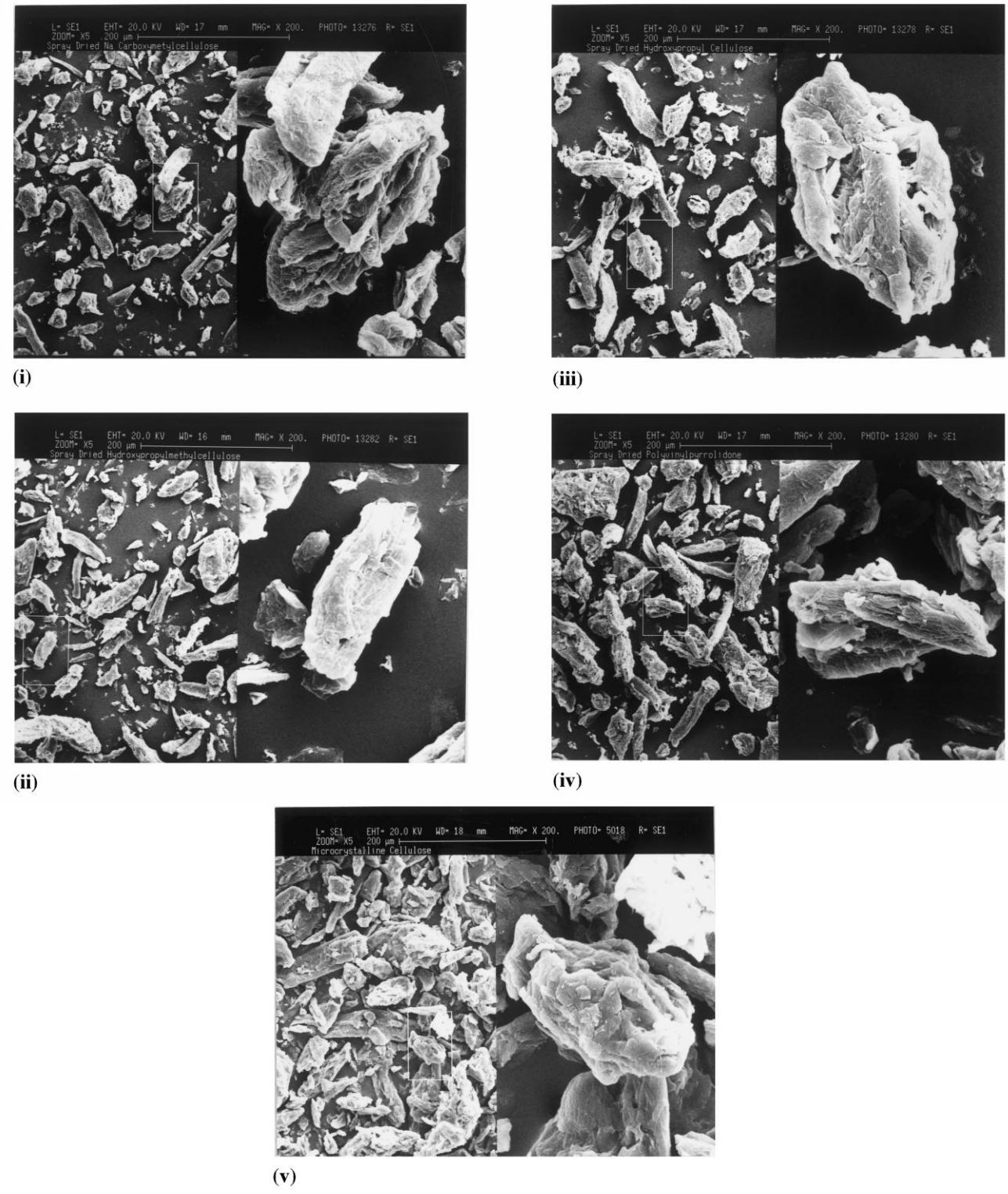


Fig. 3. Scanning electron micrographs of spray-dried polymer:MCC mixes 1:19 containing (i) NaCMC (ii) HPMC (iii) HPC and (iv) PVP, compared to (v) untreated MCC control (magnification $\times 200$, zoom $\times 5$).

dried) or Avicel® CL-611 (11.3–18.8% NaCMC content, spray-dried). Hence it is desirable that the NaCMC content be lowered as with the material developed in this project or the water content be reduced if high pellet yields of acceptable size around 1 mm are desired.

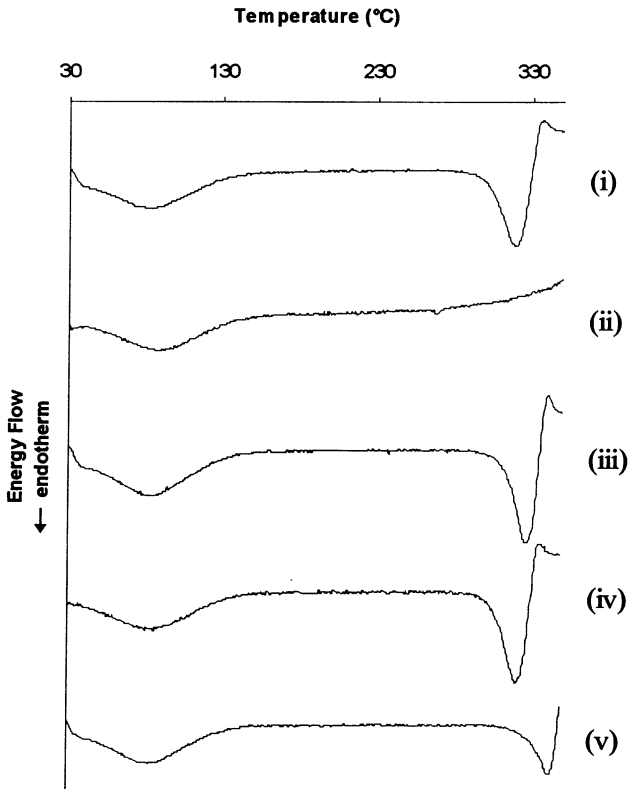


Fig. 4. DSC thermograms of (i) untreated MCC control and spray-dried polymer:MCC mixes 1:19 containing (ii) NaCMC, (iii) HPC, (iv) PVP and (v) HPMC.

3.3. SEM with energy dispersive analysis

In order to investigate the nature of the interaction between the polymer and MCC, Fig. 2 shows the distribution of sodium indicative of the location of NaCMC in polymer:MCC 1:4 prepared by physical mixing or spray-drying. A higher ratio of NaCMC/MCC to that used in pellet production was examined to better clarify the interaction. This technique was not applicable to the other polymers HPMC, HPC or PVP as they did not contain a mapable atom. It is apparent that spray-drying has caused greater size reduction probably by the disintegrant action of the soluble NaCMC on the individual crystallites bound within MCC particles in the aqueous suspension, aided by mechanical shearing of this feed in the atomizer and chamber of the spray-dryer. The more uniform distribution of NaCMC appears to be due mainly to coating of the finer MCC particles. This would facilitate increased homogeneity with lactose of the spray-dried form during the wet massing stage, favouring the observed improved yield and sphericity compared with the physical mix.

Scanning electron micrographs for all the polymer:MCC spray-dried combinations at the used ratio of 1:19 are shown in Fig. 3, compared with untreated MCC control which is also prepared commercially by spray-drying. Despite the presence of aggregates of cellulose microcrystals in all samples, a certain degree of deaggregation with size reduction relative to the untreated control is evident for all the polymers examined, the effect being probably most evident with NaCMC. Schott [4] also reported that a spray-dried combination of NaCMC:MCC 1:9 approx (Avicel® RC-951, 8.3–13.8% NaCMC content, prepared by spray-drying) promoted the disintegration of MCC bundles into their primary needle-shaped crystallites.

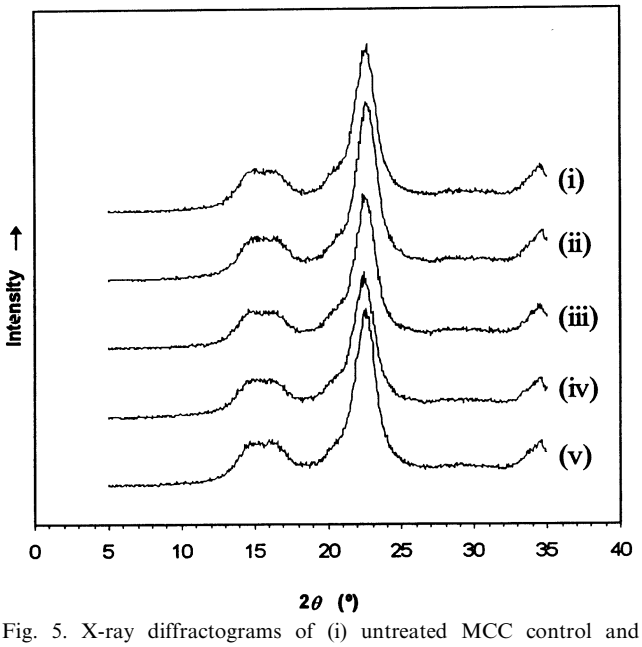


Fig. 5. X-ray diffractograms of (i) untreated MCC control and spray-dried polymer:MCC mixes 1:19 containing (ii) NaCMC, (iii) HPC, (iv) PVP and (v) HPMC.

3.4. Differential scanning calorimetry and X-ray diffraction

DSC was carried out on the spray-dried mixes of the various polymer:MCC 1:19 combinations and the traces are shown in Fig. 4, compared with an untreated MCC control. All the thermograms show a broad endotherm in the range 75–120°C, corresponding to loss of residual water. The endotherm starting at 280°C for the untreated MCC is associated with deaggregation leading to depolymerization of the cellulose. This endotherm was absent or diminished for the two most adhesive polymer blends, NaCMC and HPMC respectively, suggesting that their coprocessing with MCC caused the formation of smaller and possibly looser aggregates in agreement with the SEM studies. This smaller size and greater ease of disintegration would facilitate greater homogeneity during subsequent wet massing with lactose, leading to the observed reduced yield and sphericity in the product by promoting over-adhesion. The traces for the less adhesive spray-dried mixes of HPC or PVP with MCC resemble the control,

suggesting less interaction between the components of the mix.

X-ray diffractograms for the various spray-dried polymer/MCC combinations and untreated MCC are shown in Fig. 5. All mainly show a similar diffuse diffraction pattern characteristic of the reported amorphous behaviour of microcrystalline cellulose [5], with minor peaks at 15, 16, 22.6 and 34.6° 2θ indicating some crystallinity. This observation confirms that the spray-drying process caused a physical separation of aggregates of cellulose microcrystals and did not produce any obvious change in crystal structure.

4. Conclusions

Incorporation of hydrophilic polymers with MCC using spray-drying produced pellets in higher yield and with better sphericity, compared with physical mixing. The improvements were due to the more uniform distribution of the polymer within the spray-dried mix, which had a smaller particle size facilitating better mixing with the filler. With regard to achieving good yield with proper rounding of pellets over adequate range in water content, the less adhesive polymers HPC and PVP appear best, particularly the latter compound.

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