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Effect of batch variation and source of pulp on the properties of microcrystalline cellulose

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Summary

We have investigated the characteristics of three batches of microcrystalline cellulose supplied by the same manufacturer but differing in the manufacturing process employed and/or the type of wood pulp used as raw material. Significant differences were found as regards lignin and hemicellulose contents, percentage crystallinity (calculated from IR spectra and X-ray diffraction data), enthalpies of immersion and capacity for moisture absorption. There were close correlations between crystallinity and the parameters reflecting interaction between microcrystalline cellulose and water. All three varieties had very similar particle size distributions, but the variety obtained from non standard pulp had a significantly greater specific surface due to greater intraparticle porosity. These differences did not significantly affect parameters such as compressibility and mean yield pressure, but are nevertheless potential causes of differences in behaviour in pharmaceutical products.

Introduction

Microcrystalline cellulose, which has been widely used in the pharmaceutical industry since the 1960s, is composed chiefly of α-cellulose and is obtained from wood pulp by acid hydrolysis and subsequent spray drying (Bolhuis and Lerk, 1973). Considerable attention is currently being paid to the problem of interlot and intermanufacturer variability among microcrystalline celluloses (Whiteman and Yarwood, 1988; Parker and Rowe, 1991). The major causes of such variability are the variability of the source of pulp and of the characteristics of the manufacturing process, both as regards pulping parameters (acid or alkaline treatment, degree of degradation, bleaching sequence, etc.) and subsequent mechanical or chemical processes (milling, hydrolysis, etc.). There is now a relatively large body of information on the influence of these variables – hydrolysis regime especially – on properties such as crystallinity, degree of polymerization, water ab-

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sorption capacity, particle size and specific surface area (Soltys et al. 1984; Doelker et al., 1987; Parker et al., 1988; Whiteman and Yarwood, 1988). However, much less attention has been paid to variables related to the origin of the raw material, in spite of their evident potential importance (Kotelnikova and Petropavlovsky, 1990). Commercially available microcrystalline cellulose is derived from both gymnosperms (generally conifers) and other softwoods, and from hardwood dicotyledons. These woods differ considerably in chemical composition (proportions of cellulose, hemicelluloses and lignin) and structural organization (Harada and Côté, 1985), which affect the composition of the α-cellulose extracted and the composition and crystallinity of the microcrystalline cellulose finally produced (Kotelnikova and Petropaulovsky 1990; Baehr et al. 1991).

In this article we illustrate the effects that changing pulp type and manufacturing process can have on a wide range of properties of microcrystalline cellulose. To this end we have studied three batches of microcrystalline cellulose supplied by the same manufacturer but differing as regards the kind of pulp used and/or the conditions employed in their manufacture.

Materials and Methods

Microcrystalline cellulose

The following batches of microcrystalline cellulose (Emcocel, Edward Mendell Co.) were examined: (batch 6132) produced by the standard process using pulp from the usual source; (batch 5114) produced early in the production campaign; although derived from the standard pulp, it was considered by the manufacturer to be unrepresentative; (batch 6001) produced by the standard process but from different pulp.

Chemical analysis

Determination of lignin Lignin was assayed by the methods of Morrison (1972) and De Jaegher et al. (1985). The α-cellulose fraction was dissolved in 5 ml of 25% acetyl bromide in glacial acetic acid, and then heated for 30 min at 70°C in a thermoblock. After cooling, 5 ml of 2 N NaOH solution was added. The mixture was centrifuged at 4000 rpm for 10 min, the pellet was discarded and 0.5 ml of hydroxylamine was added to the supernatant. Lignin was determined by reading the absorbance of the final solution at 280 nm (lignin at 10 μg/ml gives an absorbance of about 0.24).

Determination of hemicelluloses Cellulose samples were hydrolyzed with 2.0 M trifluoroacetic acid (TFA) for 1 h at 121°C. The sugars released were derivatized to alditol acetates (Albersheim et al., 1967), which were determined in a Hewlett Packard Mod. 5890-II gas-liquid chromatograph equipped with a column sp 2330, 30 m.

Analysis of total sugar content Cellulose samples were hydrolyzed with 72% H_2SO_4 for 3 h at room temperature. After addition of 5.5 ml of water the mixture was heated for 2.5 h at 100°C, neutralized with $Ba(OH)_2$, brought to pH 5.5 and dried. Sugars released were analyzed as described previously.

Crystal structure

Powder X-ray diffraction Measurements were carried out at room temperature, on a Siemens X-ray diffractometer D5000 using monochromatic CuKα radiation and a scanning rate of 0.25° 2θ over the range 4–50° 2θ. Samples for analysis were prepared by pressing the powder into the cavity of a sample holder and smoothing with a glass slide.

The crystallinity index of each sample was calculated by two methods. Method 1 was implemented using a computer program to draw the demarcation line between the surface of the crystalline reflections and the diffuse halo of the amorphous regions (Doelker et al., 1987). Method 2 used intensity measurements at 22.6 and 19.0° 2θ according to Nelson and O'Connor (1964) as used by Chatrath et al. (1991)

Infrared spectroscopy Infrared spectra were obtained with a Cygnus 100, Mattson spectrophotometer by use of the potassium bromide pellet technique. The spectra were recorded over the range 400–4000 cm^{-1}. The crystallinity index was calculated using the method of Nelson and O'Connor (1964) from measurements at wavenumbers 1317 and 2900 cm^{-1}.

True density determination The true particle densities (δ_t) of the microcrystalline cellulose powders were determined using a helium-air pycnometer (Quantacrome Model PY2). Measurements were carried out at least three times for each sample.

Powder properties

Particle size analysis Particle size distributions were recorded using a Coulter LS 100 Laser Diffraction Particle Size Analyser in triplicate for each variety. The results are expressed in terms of mean surface diameter (d_S). The mean surface volume diameter (d_{SV}) was calculated from the following equation (Allen, 1978):

$$d_{SV} = \sum n_i d_i^3 / \sum n_i d_i^2$$

where n_i is the number of particles with diameter d_i from number size distributions. The particle shape factor F_S was evaluated as follows (Allen, 1978):

$$F_S = S_W \delta_t d_{SV}$$

where S_W is the specific surface area determined using nitrogen adsorption.

Scanning electron microscopy (SEM) Samples of each powder were prepared and examined using a ISI 60 scanning electron microscope. Samples to be studied were mounted on double-sided tape on aluminum stubs and coated with gold under vacuum.

Equilibrium moisture Samples of 15 g of each excipient were stored in hermetic glass bottles containing sulfuric acid solutions for maintaining 20, 40, 60, 80 and 100% RH. After equilibration the moisture contents of the samples were determined using a Shimadzu thermobalance to measure weight loss by 2 g sample after 11 min at a temperature of about 115°C (Pesonen and Paronen, 1986).

Nitrogen adsorption The specific surface area of each excipient sample was determined in a Micromeritics ASAP 2000 apparatus. Samples were first degassed by heating under vacuum for 24 h at 70°C and a pressure of 10^{-3} mmHg. Nitrogen adsorption took place at 77 K and relative pressures from 0.01 to 0.98. The specific surface area (s_W) of the samples was estimated from

$$s_W\ (m^2/g) = 4.37 V_m\ (cm^3/g)$$

where V_m is the volume of nitrogen necessary to form a monolayer which can be calculated from the BET equation (Stanley-Wood et al., 1990). Pore size distributions were calculated from the nitrogen adsorption isotherms by the BJH method (Stanley-Wood, 1983).

Immersion calorimetry Immersion calorimetry was carried out on prepared microcrystalline cellulose samples using a Tronac model 458 Solution Calorimeter described previously (Parker and Rowe, 1991) Samples of microcrystalline cellulose of differing moisture contents were prepared by storage over saturated salt solutions or in glass desiccator jars.

Measurements were carried out in duplicate for each level of moisture, and graphs of enthalpy of immersion against moisture content of sample could then be plotted. These curves were characterized by the value of the enthalpy of immersion for 12% humidity (E_{12}) and by the value estimated by extrapolation for the dry powder (E_0) (Parker, 1989).

Flow properties

Bulk density determination A Hosokawa powder tester was used to measure the tapped density as particles in a powder were rearranged, packed and compacted at 50 taps/min for periods of time up to 20 min. After determination of the tapped bulk density values, the results could be used to calculate the indices of flowability and floodability and the compressibility (Thomsom, 1984).

Compression properties

The compression properties of the cellulose materials were tested by preparing 200 mg tablets 9 mm in diameter in a single punch machine equipped with transducers (Martínez-Pacheco et al., 1985). Tablets were compressed to 25% of initial volume at a rate of 41 tablets/min. Powders were stored under two different moisture conditions (ambient and after storage in an oven for 48 h at 50°C).

Mean yield pressures underload were determined using Heckel plots of the data from compression force-displacement cycles (Humbert-Droz et al., 1982).

Results and Discussion

All three batches of microcrystalline cellulose studied contained significant quantities of impurities derived from the wood of origin (Table 1). Hydrolysis with TFA, which primarily breaks down the hemicellulose surrounding cellulose fibers in wood, released small quantities of xylose and mannose from xylans and mannans respec-

TABLE 1

Characteristics of three batches of microcrystalline cellulose differing in pulp source and/or processing conditions (mean values (standard deviations))

	Emcocel 6132	Emcocel 5114	Emcocel 6001
Lignin (%):	0.70 (0.09)	0.82 (0.05)	0.55 (0.08)
Hemicelluloses (TFA)			
Xylose (%)	0.32 (0.06)	0.19 (0.02)	0.39 (0.06)
Mannose (%)	0.12 (0.02)	0.08 (0.01)	0.17 (0.01)
Glucose (%)	1.68 (0.25)	1.00 (0.02)	1.46 (0.11)
Total sugars (H_2SO_4)			
Xylose (%)	3.9	3.7	4.1
Mannose (%)	7.1	4.9	5.3
Arabinose (%)	1.4	0.5	0.5
Galactose (%)	1.7	1.2	1.8
Glucose (%)	86.0	89.8	88.3
α (%) (method 1)			
X-ray diffraction	64.3	63.3	61.0
α (%) (method 2)			
X-ray diffraction	86.2	84.9	83.9
$\alpha_{1371}/\alpha_{2900}$			
IR spectroscopy	58.3	56.0	48.2
True density (g/cm^3)	1.543 (0.017)	1.549 (0.016)	1.549 (0.018)
Laser light scattering			
d_s (μm)	57.6 (7.29)	57.5 (3.24)	58.7 (1.30)
d_{sv} (μm)	75.39	75.51	75.30
Shape factor	114.00	123.98	138.24
Surface area (m^2/g)	0.98 (0.04)	1.06 (0.10)	1.19 (0.01)
Equilibrium moisture (%)			
(65% RH)	6.73	7.41	8.27
E_0 (−J/g)	47.18	48.28	52.61
E_{12} (−J/g)	2.57	2.53	2.99
Compressibility (%)	35.70 (0.55)	37.50 (0.72)	36.15 (0.70)
Flowability index	50.00	47.00	54.00
Floodability index	78.90	78.00	76.00
Mean yield pressure (MPa)	41.96 (1.50)	44.27 (0.41)	47.13 (1.92)
at moisture content	4.20	4.56	4.13
Mean yield pressure (MPa)	68.97 (0.83)	73.54 (0.95)	75.78 (1.73)
at moisture content	3.76	3.56	3.88

tively; a small quantity of glucose was also present, probably due to the peeling of the external layer of cellulose fibers. Hydrolysis with sulfuric acid to break down the cellulose fibers themselves produced larger quantities of xylose and mannose (the latter especially), probably derived from hemicellulose trapped among the fibers, together with significant quantities of galactose and arabinose from arabino-galactans. The manose/xylose ratios for the three varieties of microcrystalline cellulose reflect their coniferous origin (Baehr et al., 1991). The significant influence of processing differences is shown by batch 5114 having considerably less hemicellulose but considerably more lignin than the standard product (batch 6132), while the influence of pulp source is evident in the greater hemicellulose content and lower lignin content of batch 6001. In a previous study of microcrystalline celluloses (Baehr et al., 1991), compositions similar to those of Table 1 were found, although with less hemicellulose.

It should be pointed out that the non-cellulose sugars and lignin contents of all three batches imply failure to comply with the α-cellulose content specifications of the US, British and European Pharmacopeias (97–102%). The hydrophobic nature of lignin, and the swelling properties derived from the hydrophilic character of hemicellulose, suggest the desirability of introducing more specific purity requirements for microcrystalline celluloses.

The crystallinity of microcrystalline cellulose, which has significant technological implications (Stamm, 1981), has been reported to vary widely both from one manufacturer to another and from lot to lot (Doelker et al., 1987). Several methods for evaluating crystallinity have been mentioned in the literature (Nakai et al., 1977; Doelker et al., 1987); in this work we used X-ray diffraction and infrared spectroscopy. The X-ray scans obtained all gave the peaks at 15, 16 and 22.6° 2θ that are characteristic of cellulose I. However, the degree of crystallinity determined depended greatly on the method used (Table 1), which no doubt largely explains the disparity among the reported crystallinities of microcrystalline cellulose (Nakai et al., 1977; Soltys et al., 1984). The three methods nevertheless correlated well (Fig. 2), and are therefore all valid for comparing different microcrystalline celluloses. In this work,

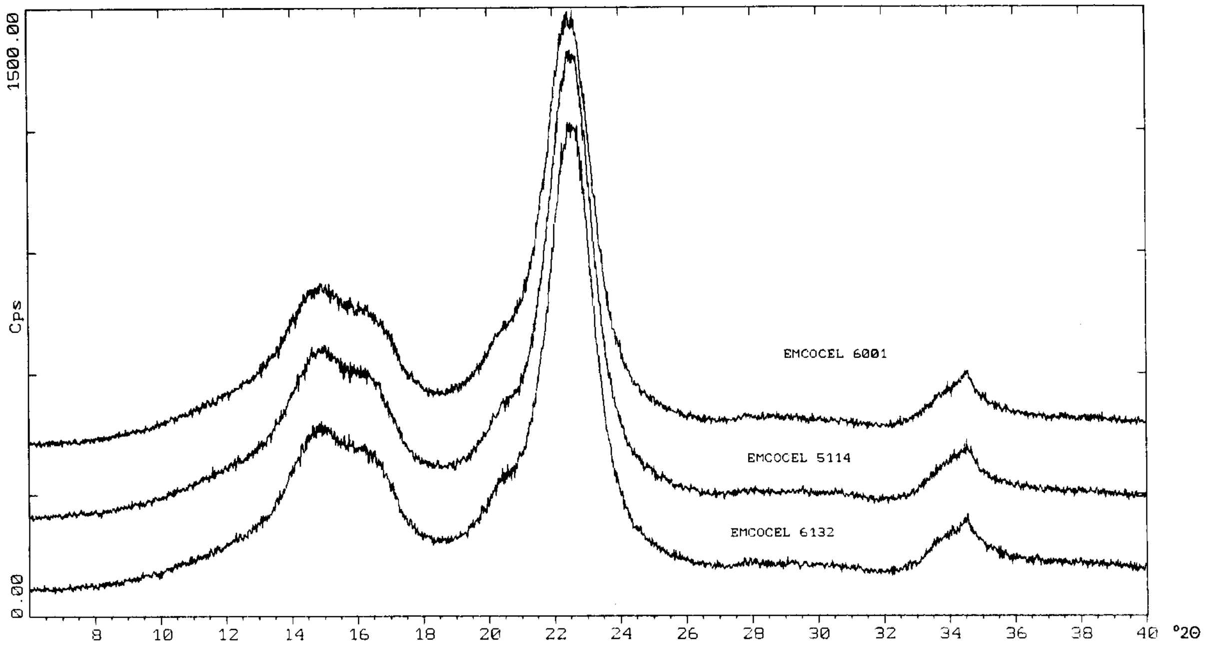

Fig. 1. X-ray diffraction scans.

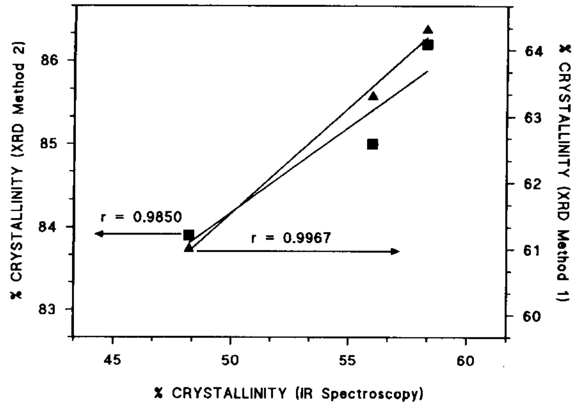

Fig. 2. Correlations among crystallinity indices.

the standard product (batch 6132) was the most crystalline, and the least crystalline was the product obtained from non-standard pulp (batch 6001). Crystallinity thus appears to depend more on pulp source than on processing, whereas the reverse was seen above to hold for chemical composition. The differences in crystallinity did not result in differences in true density, which was virtually identical for all three batches (Table 1).

The particle size distributions of the three batches (Fig. 3), and hence their mean surface diameters (Table 1), were virtually identical. Microphotographs show all three to consist of the elongated fibre-like particles typical of microcrystalline cellulose (Fig. 4). The specific surface area determined from nitrogen adsorption measurements was nevertheless significantly greater for batch 6001 than for the other batches (Table 1). The pore size distributions calculated from the nitrogen adsorption isotherms showed total pore volume to be small for all three batches, in agreement with previous reports (Stanley-Wood et al.,

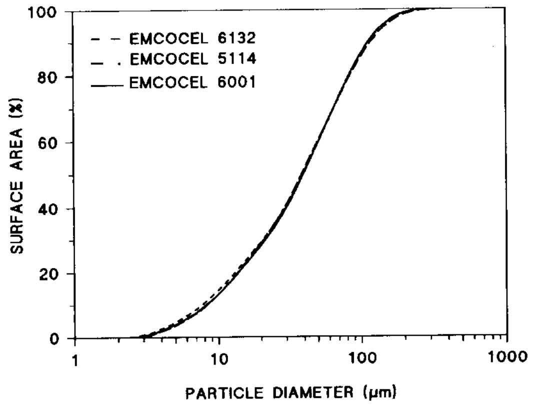

Fig. 3. Particle size distributions determined by laser light scattering.

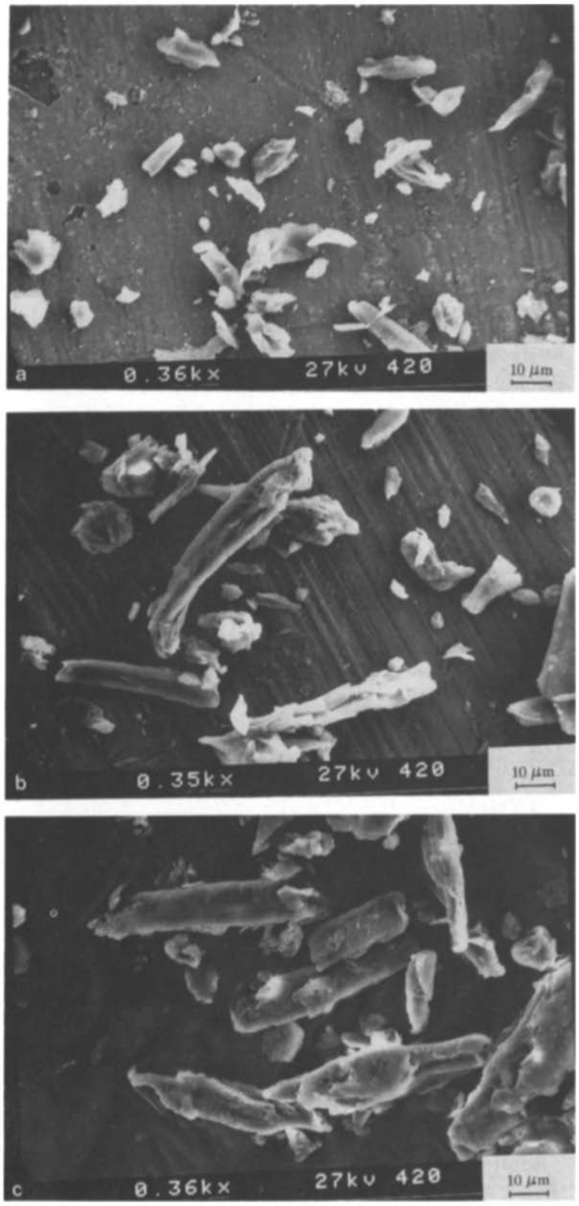

Fig. 4. Microphotographs of samples of the three batches of microcrystalline cellulose studied. (a) Emcocel 6132; (b) Emcocel 5114; (c) Emcocel 6001.

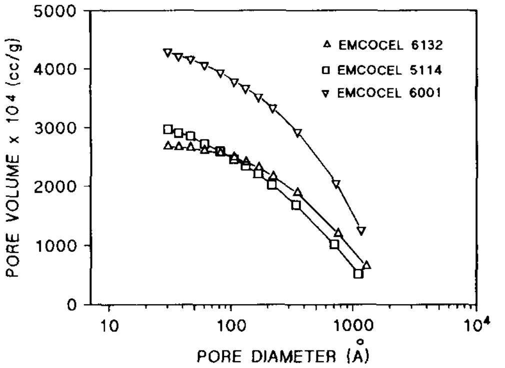

Fig. 5. Pore size distribution calculated from nitrogen adsorption isotherms by the BJH method.

1990), but explained the greater specific area of batch 6001 (and its greater form factor; see Table 1) as due to its greater number of smaller pores (Fig. 5). Pore structure and particle form may thus be significantly influenced by the kind of wood from which the source pulp is derived.

Many technologically relevant properties of microcrystalline cellulose depend on its interaction with water (Khan et al., 1988; Staniforth et al., 1988). The equilibrium moisture-humidity curves of the three batches studied in this work (Fig. 6) are very similar to each other and to those of other varieties (Handbook of Pharmaceutical Excipients, 1986). The differences among the three (batch 6001 always had the highest moisture content) are greatest for relative humidities of 60–80%, and can be attributed to the differences in crystallinity, with which the moisture contents at 65% relative humidity (Nelson and O'Connor, 1964) exhibit good negative correlation ($r = -0.9719$; see Fig. 7). These results are in keeping with the theory that water molecules are excluded from the crystalline nucleus of the cellulose fibers, being retained by their amorphous 'envelope' (Khan et al., 1988).

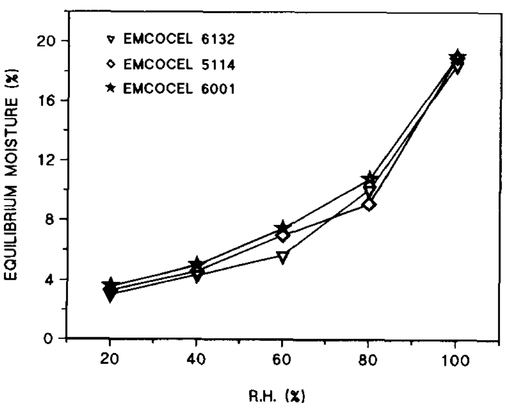

Fig. 6. Equilibrium moisture-humidity curves.

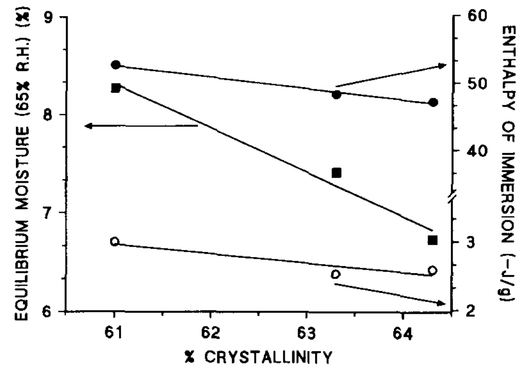

Fig. 7. Correlation of moisture content (at 65% relative humidity) (■), enthalpy of immersion at zero moisture content (●) and enthalpy of immersion at 12% moisture content (○) with crystallinity (as measured by X-ray diffraction method 1).

The plots of enthalpy of immersion against moisture content obtained for each batch by immersion calorimetry (Fig. 8) are, like the equilibrium moisture-humidity curves, very similar to each other and to those reported for other varieties (Hollenbeck et al., 1978; Parker and Rowe 1991). Again, batch 6001 has the highest enthalpy for all values of moisture content, a finding which the close negative correlation between both E_{12}

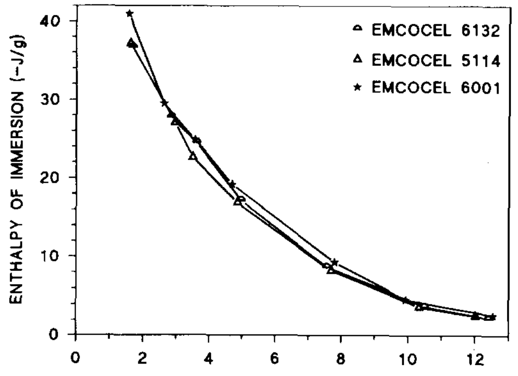

Fig. 8. Dependence of enthalpy of immersion on moisture content.

and E_0 and crystallinity ($r = -0.9994$ and $r = -0.9292$ respectively; see Fig. 7) shows may be attributed to this later factor. Once more, these results are in keeping with the notion that it is amorphous glucose anhydride with which water molecules interact, rather than the crystalline core (Khan et al., 1988). Surprisingly, there was no significant correlation between E_{12} and E_0 and lignin (which is hydrophobic) or hemicellulose (which is hydrophilic) content.

Among the most important characteristics of microcrystalline cellulose as an excipient are those related to flow and compression. The compressibility, flowability and floodability of the three batches studied were very similar (Table 1), and compressibility was likewise similar to values reported for other varieties. Mean yield pressures were also within the reported range for microcrystalline cellulose, and show that densification was achieved largely as the result of particle deformation. The small but significant differences in yield pressure among the three batches are attributed to differences among their moisture contents when yield pressures were measured (Table 1), a hypothesis supported by the variation in yield pressure with moisture for each individual batch (Roberts and Rowe, 1987).

Conclusions

In conclusion, the results of this study show that the chemical composition and physical structure of microcrystalline cellulose depend significantly upon the characteristics of both the raw materials used and manufacturing conditions. Though the observed differences appear not to affect the properties customarily used to characterize microcrystalline cellulose, they should be borne in mind as potential causes of non-uniform behaviour and with a view to the establishment of more rigorous quality standards.

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