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# Influence of microcrystalline cellulose source and batch variation on the tabletting behaviour and stability of prednisone formulations

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## Summary

The characteristics of prednisone tablets formed by direct compression with six previously characterized microcrystalline celluloses (MCCs) were studied. MCCs of similar particle size produced tablets with similar mechanical and microstructural properties, but prednisone dissolution rate varied significantly with MCC particle size and chemical composition. When stored under conditions of high relative humidity, all formulations underwent significant changes in mechanical and drug release properties, which is attributed to interaction between MCC and water.

## Introduction

In recent years, a number of technological problems, especially with solid dosage forms, have been attributed to the inter-batch and/or inter-manufacturer variability of excipients. Many studies of these problems have shown their effects in particular areas or have simply drawn attention to the heterogeneity of the raw materials from which the excipients are derived (Pesonen and Paronen, 1986; Doelker et al., 1987). However, the formulation of rational criteria for the interchangeability of excipient lots or varieties requires a more comprehensive analysis that identifies the origin of the variation (raw material, manufacturing process, etc.) and determines the influence of observed differences on the properties of the dosage forms in which the excipients are to be used. In the preceding papers (Landín et al., 1993a,b) we compared a series of batches and varieties of microcrystalline cellulose of various origins as regards their chemical composition, crystalline structure, interaction with water, granulometry and rheological properties. In the work reported here, the same MCCs as in the earlier

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studies were used as filler binders in prednisone tablets whose mechanical, microstructural and drug release properties were evaluated both immediately after their preparation and after storage for 2 or 4 months at a relative humidity of 90%.

Prednisone was chosen as the active principle for these studies because its poor flow properties and poor solubility in water make the mechanical and drug release properties of prednisone tablets highly sensitive to the technological characteristics of their formulation (Gómez-Amoza and Stanley-Wood, 1991; Landín et al., 1992). A previous study (Martínez-Pacheco et al., 1989) has likewise shown the tendency of directly compressed prednisone-MCC tablets to deteriorate when stored at 20°C and 90% relative humidity, which is why these conditions were chosen for the shelf-life study.

## Materials and Methods

*Active principle and excipients*

Micronised prednisone (lot 035, J. Escuder, Spain); (microcrystalline celluloses) Avicel PH 101 (FMC, Ireland), Emcocel batches 6132, 6001 and 5114 (Edward Mendell, Finland), Unimac MG 100 (Unitika Rayon, Japan) and an MCC from India supplied by Steetley-Berk (U.K.); and magnesium stearate B.P. (lot 548, C. Barcia, Spain) were obtained from the indicated sources. Some of the characteristics of these MCCs, determined in previous work (Landín et al., 1993a,b), are listed in Table 1.

*Formulations*

Formulations were made from mixtures of identical composition (microcrystalline cellulose 94.5%, prednisone 5% and magnesium stearate 0.5%), except that each contained a different variety of microcrystalline cellulose. The mixtures were blended in a Turbula T2C mixer for 15 min at 30 rpm. Tablets were compressed using a maximum compaction force of 2500 N in a Korsch EK-O excentric press equipped with Kistler 9031A piezoelectric pressure transducers and a Peney & Giles type LCP displacement transducer, and interfaced to a Hewlett Packard 85 computer via an HPIB data monitoring system (Martínez-Pacheco et al., 1985). The press was fitted with 9 mm diameter flat punches to prepare 200 mg tablets at rate of 55 tablets per min, except for the formulation with the Indian MCC. Because of the poor flow properties associated with its small particle size (Table 1), which prevented uniform filling of the die and so caused excessive tablet weight variation, tablets with MCC from India were prepared with the same maximum compression force (2500 N) but at a slower rate (8 tablets/min), and tablets deviating by more than 7.5% from the theoretical 200 mg were discarded.

*Characterization of tablets*

Tablets of each of the formulations were subjected to the following tests:

*Dimensions* The thickness and diameter of six tablets were determined with a digital calibrator (Carl Marh).

*Weight* The weights of 20 tablets were deter-

TABLE 1

*Chief characteristics of MCCs studied (data from Landín et al., 1993a,b)*

| Microcrystalline cellulose | Country of origin | Lignin content (%) | Crystallinity (%) | Surface area ($m^2/g$) | Mean particle size ($\mu m$) | Compressibility (%) |
|---|---|---|---|---|---|---|
| Avicel PH 101 | Ireland | 0.66 | 62.9 | 1.15 | 47.3 | 39.17 |
| Emcocel (6132) | Finland | 0.70 | 64.3 | 0.98 | 57.6 | 36.11 |
| Emcocel (6001) | Finland | 0.55 | 61.0 | 1.19 | 58.7 | 36.15 |
| Emcocel (5114) | Finland | 0.84 | 63.3 | 1.06 | 57.5 | 37.50 |
| Unimac MG 100 | Japan | 0.35 | 62.1 | 1.13 | 39.9 | 42.02 |
| MCC India | India | 0.95 | 61.3 | 1.58 | 22.4 | 48.52 |

mined individually and the mean weight and coefficient of variation calculated.

*Tensile strength* This was calculated for each of six tablets from the equation (Summers et al., 1977):

$$\text{Tensile strength} = \frac{2 \cdot CS}{\pi \cdot D \cdot E}$$

where CS is the crushing strength determined in an Erweka TB24 apparatus, $D$ denotes the diameter of the tablet and $E$ is its thickness.

*Friability* Weight loss through friability was determined for 10 tablets after 15 min an Erweka TAP apparatus at 25 rpm.

*Disintegration time* The distintegration times of six tablets were measured individually in distilled water in an apparatus (Turu Grau, Spain) fulfilling the USP XXI specifications.

*Dissolution rate* The dissolution rate of prednisone was determined for six tablets in an apparatus (Turu Grau, Spain) following the procedure established in the USP XXI. The active principle dissolved was determined spectrophotometrically at 239 nm and the dissolution rate was characterized by means of the dissolution efficiency in 30 min (Khan and Rhodes, 1972).

*Microstructural characterization* Micropore structure was investigated by mercury intrusion porosimetry with a Micromeritics 9305 Pore Sizer with a 3 ml penetrometer for solids. Working pressures covered the range 0.6–25000 lb/inch$^2$. The total porosity and average pore diameter were determined three times for each formulation.

*Statistical analysis*

The statistical significance of differences among the various formulations as regards parameters of interest was estimated by one-way analysis of variance. Whenever $F$ values indicated the existence of significant inter-formulation differences, identification was by comparison of the least significant difference at the $p < 0.01$ level (LSD) with the differences between the means of the formulations. Where appropriate, formulations are presented in the text using Duncan's underlying convention, i.e., ranked by their means for the parameter in question, with formulations whose means differ by less than LSD linked by a continuous underline (Walpole and Myers, 1989).

*Storage of tablets*

Tablet formulations were stored at 20°C in hermetically sealed containers containing a sulphuric acid solution providing a relative humidity of 90%. Samples were taken after 2 and 4 months and were characterized as before.

## Results and Discussion

Table 2 lists the characteristics of the formulations prepared. Though analysis of variance detected significant inter-formulations variation in tensile strength ($F = 35.09$ with 5 and 30 d.f.), it was due entirely to the low value for the tablets with MCC from India, all the other formulations having very similar tensile strengths. The Indian MCC tablets were also much more variable than

TABLE 2

*Mean values (with SDs in parentheses) of parameters characterizing formulations made up with the various MCCs studied*

| Formulation | Moisture content (%) | Tensile strength (MPa) | Friability (%) | Disintegration time (s) | Dissolution efficiency | Total porosity (%) | Mean pore diameter ($\mu$m) |
|---|---|---|---|---|---|---|---|
| Avicel PH 101 | 4.93 | 1.23 (0.17) | 0.22 | 9 (1.38) | 0.46 (0.02) | 29.38 (0.14) | 0.23 (0.03) |
| Emcocel (6132) | 5.59 | 1.11 (0.11) | 0.03 | 10 (0.82) | 0.42 (0.05) | 32.97 (2.15) | 0.23 (0.03) |
| Emcocel (6001) | 5.54 | 1.15 (0.05) | 0.08 | 13 (0.75) | 0.31 (0.07) | 33.09 (0.53) | 0.24 (0.02) |
| Emcocel (5114) | 4.93 | 1.02 (0.09) | 0.29 | 11 (1.03) | 0.50 (0.08) | 35.88 (0.62) | 0.27 (0.01) |
| Unimac MG 100 | 5.21 | 1.11 (0.05) | 0.70 | 15 (1.94) | 0.18 (0.05) | 34.99 (2.16) | 0.26 (0.01) |
| MCC India | 5.41 | 0.45 (0.56) | 0.85 | 24 (6.45) | 0.12 (0.01) | 42.12 (0.73) | 0.39 (0.01) |

the others in both tensile strength and weight (in spite of the weight selection procedure noted in Materials and Methods), and was the only formulation to exceed the generally accepted limit of 0.8% for loss of weight in the friability test. All these deficiencies of the tablets with MCC from India may be attributed to the poor flow properties of the Indian MCC (Table 1). As in a study of other varieties of cellulose (Pesonen and Paronen, 1986), there was no significant correlation between tensile strength and friability.

The microporous structures of the tablets were characterized by total porosity and mean pore diameter (Table 2). One-way analysis of variance of total porosities showed significant interformulation variation ($F = 9.05$ with 5 and 6 d.f.) which, like the variation in tensile strength (which it explains), was due largely to the highly porous tablets with the Indian MCC. Total porosity was in fact closely correlated with tensile strength ($r = -0.9448$). Similar remarks hold for the mean pore diameter results, which support the hypothesis (Landín et al., 1992, 1993c) that the more open porous structure of formulations with MCC from India is due to this MCC having a smaller particle size and the poorer flow and compactation properties than the others.

As is usual with MCC formulations (Doelker et al., 1987), all the disintegration times were very short. Inter-formulation difference in this parameter are therefore of little practical relevance.

The various formulations studied differed widely as regards the rate of release of prednisone (Fig. 1). Tablets with MCC from India or Unimac MG-100 (from Japan) released the active principle very slowly, and there were significant differences among those made up with the three batches of Emcocel. The LSD for the 30 min prednisone release efficiency values ($F = 50.85$ with 5 and 30 d.f.) groups the MCCs as follows:

| | | |
|---|---|---|
| MCC from India | Unimac MG-100 | Emcocel batch 6001 |
| Emcocel batch 6132 | Avicel PH-101 | Emcocel batch 5114 |

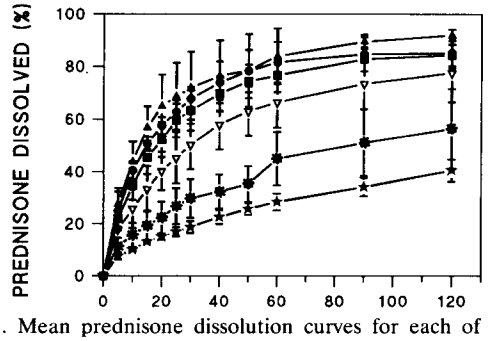


Fig. 1. Mean prednisone dissolution curves for each of the formulations made up with the various MCCs studied; (●) Avicel PH-101; (■) Emcocel 6132; (▽) Emcocel 6001; (▲) Emcocel 5114; (*) Unimac MG-100; (☆) MCC from India.

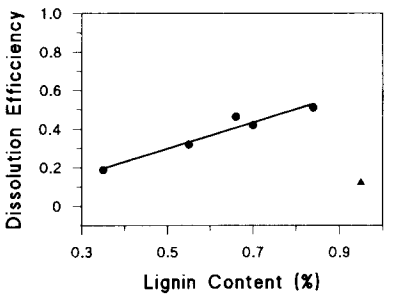


Fig. 2. Correlation between prednisone dissolution efficiency and MCC lignin content ($r = 0.9696$) among all the formulations studied except that made up with MCC from India (▲).

The fact that Emcocel batch 6001 only differed from the standard product (batch 6132) as regards the wood from which it was produced suggests that this factor is of importance for the release properties of tablets prepared with MCC. More specifically, joint analysis of the MCC characteristics (Table 1) and prednisone release data showed that MCC lignin content, which depend on the wood of origin and the MCC manufacturing process (Landín et al., 1993a,b), was closely correlated with dissolution efficiency if the MCC from India was excluded (Fig. 2). The reason for this correlation may be that lignin, being hydrophobic and located mainly in the outer region of the MCC fibrous (Harada and Côte, 1985), may alter cellulose-cellulose and/or cellulose-prednisone interactions and hence the process of drug release. The anomalous behaviour of the MCC from India may be due either to its small

TABLE 3

*Mean values (with SDs in parentheses) of parameters characterizing formulations made up with the various MCCs studied, after 2 month storage at 20°C and 90% relative humidity*

| Formulation | Weight variation (%) | Tensile strength (MPa) | Friability (%) | Disintegration time (s) | Dissolution efficiency | Total porosity (%) | Mean pore diameter ($\mu$m) |
|---|---|---|---|---|---|---|---|
| Avicel PH 101 | 5.76 | 0.50 (0.08) | 1.53 | 17 (0.89) | 0.37 (0.05) | 36.56 (1.24) | 0.28 (0.03) |
| Emcocel (6132) | 5.36 | 0.53 (0.02) | 1.19 | 14 (0.54) | 0.38 (0.09) | 37.50 (1.20) | 0.24 (0.02) |
| Emcocel (6001) | 5.07 | 0.70 (0.07) | 1.42 | 19 (1.94) | 0.14 (0.01) | 35.47 (1.06) | 0.28 (0.00) |
| Emcocel (5114) | 5.76 | 0.50 (0.05) | 1.38 | 15 (1.26) | 0.39 (0.20) | 37.15 (1.57) | 0.26 (0.01) |
| Unimac MG 100 | 5.30 | 0.56 (0.08) | 2.03 | 20 (1.87) | 0.15 (0.03) | 36.76 (1.20) | 0.28 (0.02) |
| MCC India | 2.50 | 0.28 (0.04) | 2.73 | 37 (9.71) | 0.09 (0.01) | 41.16 (3.42) | 0.31 (0.06) |

particle size or the tablets with this MCC having been produced at a lower punch rate than those made up with the other MCCs studied.

Tables 3 and 4 list the parameters characterizing the formulations after 2 and 4 months storage, respectively at 20°C and 90% relative humidity. All the tablets increased considerably in weight and size (especially in the axial direction) due to absorption of moisture. Khan et al. (1988) reported similar behaviour by tablets like those studied in this work. Moisture uptake also altered the microporous structure of the tablets, as was reflected by the increase in total porosity values. This process, which is attributed to the adsorbed water breaking hydrogen bonds between MCC fibres and so creating more open structures, caused serious deterioration in the mechanical properties of the tablets, increasing friability and reducing tensile strength (Fig. 3). The deterioration affected all the formulations to very similar extents, and was already complete after 2 months storage, with no significant further gain in moisture took place thereafter. Other authors have also noted the harmful effect of humidity on the mechanical properties of MCC tablets (Nyquist and Nicklasson, 1983; Khan et al., 1988).

Storage likewise considerably reduced the rates at which prednisone was released from all the formulations (Fig. 4; see also the dissolution efficiency data of Tables 3 and 4). The formulations differed as regards the change in dissolution rate during the first two months' storage, but were all very similar as regards the change undergone over the total 4 months of the study. Like the changes in mechanical properties, the changes in dissolution efficiency appear to be directly attributable to increased moisture content (Fig. 3). Fig. 5 shows, for each formulation studied, the

TABLE 4

*Mean values (with SDs in parentheses) of parameters characterizing formulations made up with the various MCCs studied, after 4 month storage at 20°C and 90% relative humidity*

| Formulation | Weight variation (%) | Tensile strength (MPa) | Friability (%) | Disintegration time (s) | Dissolution efficiency | Total porosity (%) | Mean pore diameter ($\mu$m) |
|---|---|---|---|---|---|---|---|
| Avicel PH 101 | 6.28 | 0.60 (0.05) | 1.34 | 18 (1.86) | 0.31 (0.09) | 36.50 (0.61) | 0.27 (0.04) |
| Emcocel (6132) | 4.69 | 0.49 (0.05) | 1.32 | 15 (2.19) | 0.32 (0.08) | 32.00 (5.33) | 0.34 (0.06) |
| Emcocel (6001) | 3.78 | 0.62 (0.05) | 1.00 | 19 (1.41) | 0.21 (0.04) | 35.61 (2.47) | 0.25 (0.01) |
| Emcocel (5114) | 5.60 | 0.56 (0.06) | 1.64 | 18 (1.33) | 0.27 (0.03) | 34.17 (0.28) | 0.34 (0.02) |
| Unimac MG 100 | 5.06 | 0.61 (0.04) | 1.91 | 17 (1.79) | 0.12 (0.03) | 34.78 (1.84) | 0.28 (0.02) |
| MCC India | 1.49 | 0.32 (0.06) | 1.87 | 40 (8.67) | 0.11 (0.02) | 47.12 (2.12) | 0.43 (0.02) |

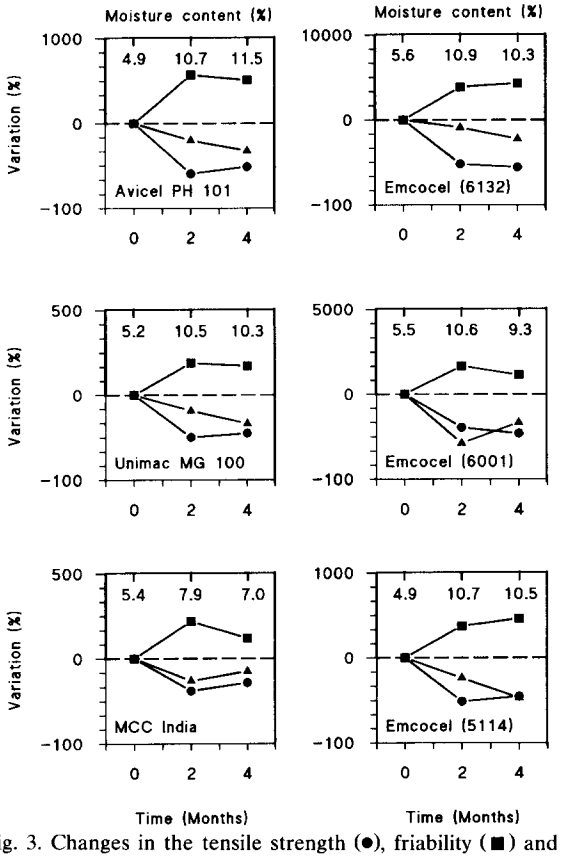


Fig. 3. Changes in the tensile strength (●), friability (■) and prednisone dissolution efficiency (▲) of the formulations during storage at 20°C and 90% relative humidity.

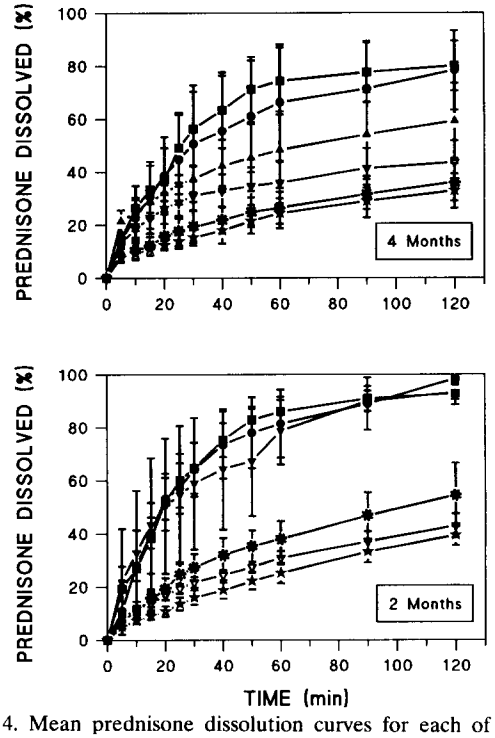


Fig. 4. Mean prednisone dissolution curves for each of the formulations made up with the various MCCs studied after 2 and 4 month storage; (●) Avicel PH-101; (■) Emcocel 6132; (△) Emcocel 6001; (▲) Emcocel 5114; (∗) Unimac MG-100; (☆) MCC from India.

correlation between dissolution efficiency and the enthalpy of immersion of the corresponding MCC at the same moisture content, as obtained by interpolation of previously published enthalpy-moisture data (Landín et al., 1993a,b). Though the correlations are only valid for a given formulation (due to the influence of other variables, including those discussed above, on dissolution efficiency), these results confirm the importance of MCC moisture content for the release of active principles like prednisone.

## Conclusions

Analysis of the mechanical properties of prednisone-MCC tablets produced by direct compression showed no significant differences among formulations made up with MCC varieties of similar particle size. The rate of release of prednisone, on the other hand, clearly depended on MCC variety, which is attributed to differences in the

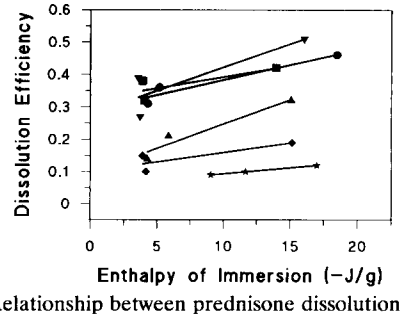


Fig. 5. Relationship between prednisone dissolution efficiency and MCC enthalpy of immersion (see text). (●) Avicel PH-101 ($r = 0.9616$); (■) Emcocel 6132 ($r = 0.7956$); (▲) Emcocel 6001 ($r = 0.9669$); (▼) Emcocel 5114 ($r = 0.8607$); (◆) Unimac MG-100 ($r = 0.8208$); (☆) MCC from India ($r = 0.9999$).

raw materials and processes used in the manufacture of the MCCs; in particular, for MCCs of similar particle size, there was close correlation between MCC lignin content and the prednisone release rate.

All the formulations studies underwent considerable changes in mechanical, microstructural and drug release properties during storage. These changes were related to absorption of moisture, and can be interpreted in terms of changes in properties characterizing MCC-water interactions, such as enthalpy of immersion.

In conclusion, the results of this work, which extends two previous studies (Landín et al., 1993a,b), confirm the importance of characterizing as fully as possible the raw materials used for products such as MCCs in order to account for the effects of inter-lot and inter-manufacturer variability on the quality of dosage forms in which they are used.

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