DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(3), 355-368 (1992)

COMPARISON OF TWO VARIETIES OF MICROCRYSTALLINE CELLULOSE AS FILLER-BINDERS I. PREDNISONE TABLETS

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SUMMARY

A comparative study of two varieties of microcrystalline cellulose (Avicel PH 101 and Avicel PH 102) as excipients in direct compression prednisone tablets has been carried out. The effects of compression force, proportion of drug/excipient and variety of cellulose (defined by means of mean particle size) on the structural, mechanical and release properties of the tablets were studied. Differences were observed in the behaviour of the two varieties of cellulose affecting all the properties analyzed. These differences diminished, and disappeared in some cases, when 10% prednisone was present. The different degrees of interparticle association and the relations between the structural, mechanical and drug release properties of the tablets explain the differences observed.

INTRODUCTION

Microcrystalline celluloses form a group of excipients widely used in direct compression. There is considerable information available concerning the flow and binding properties of the marketed varieties, which differ in the size and structure of their particles (1) (2). The drawbacks of the first to appear on the market (3) (4) their flow properties and predominating compression mechanisms are well known too (5). Furthermore, there have been many studies of the mechanical properties of tablets fabricated using these materials (6) (7). But, much less information is available on the relations between their

microstructural, mechanical and drug release properties. This forms the rationale for this contribution, which is a comparative study of two of the varieties of microcrystalline cellulose (Avicel PH 101 and Avicel PH 102) most frequently used in direct compression tablets. The active principle used was prednisone, an example of a drug of low hydrosolubility that compresses by plastic deformation (8).

MATERIALS AND METHODS

Active principle and excipients

Micronised Prednisone (lot 035, J. Escuder, Spain).

Microcrystalline cellulose: Avicel PH 101 (lot 852, C. Barcia, Spain) with nominal mean particle size of 50 μm and Avicel PH 102 (lot 831, C. Barcia, Spain) with nominal mean particle size of 100 μm.

Magnesium stearate B.P. (lot 548, C. Barcia, Spain).

Formulations

The 18 formulations studied are described in Table 1. The variety of microcrystalline cellulose used (V), percentage of active principle (D) and maximum compression force (CF) applied during elaboration were varied. Mixtures were prepared in a Túrbula T2C mixer at 30 r.p.m. for 15 min. In all cases, 0.5 % w/w of magnesium stearate was added. Tablets were obtained by direct compression in a Korsch EKO machine equipped with 9 mm flat punches and piezoelectric transducers (9). For all the formulations, tablet weight was adjusted to 200 mg and the production rate to 33 tablets/min.

Characterization of the compression process

For each formulation, once production had stabilized, three force-displacement compression cycles were recorded at the level of the upper punch, each one defined by at least 25 numerical values. The net work of compression (NW) and the energy lost by elastic deformation (WE) were calculated from these data (10).

Characterization of the tablets

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

Dimensions. The thickness and diameter of 6 tablets were determined with a digital calibrator Carl Mahr 18E (Germany).

Weight. The weight of 20 tablets was determined individually and the mean weight and coefficient of variation (CV) calculated.

TABLE 1

Differential characteristics of the formulations studied and mean values of the parameters used to characterize them.

Formulation	Avicel	% Prednisone	CF N	CV %	Fr %	C.S kg	DT s	DE	NW Jules	WE Jules	VW ml/g	TP %	DG µm
A		0	900	0.48	0.19	3.0	13	-	0.78	0.12	1.48	31.45	1.21
B		0	1700	1.40	0.00	6.7	16	-	1.23	0.23	1.18	30.16	0.93
C		0	2500	0.97	0.00	9.1	17	-	1.70	0.47	1.05	28.36	0.74
D		5	900	1.35	1.60	2.6	4	0.8826	0.49	0.11	1.64	32.41	1.12
E	PH 101	5	1700	1.41	0.44	5.3	11	0.5059	1.15	0.26	1.58	32.28	0.73
F		5	2500	1.99	0.23	8.5	15	0.2259	1.70	0.36	1.49	27.78	0.55
G		10	900	0.49	2.88	2.4	10	0.9123	0.51	0.06	1.60	33.82	0.94
H		10	1700	0.77	0.51	5.8	12	0.7905	1.21	0.21	1.52	31.48	0.60
I		10	2500	0.78	0.25	8.3	16	0.4316	1.38	0.37	1.26	25.10	0.39
J		0	900	0.67	0.45	4.5	16	-	0.47	0.09	1.29	32.23	0.97
K		0	1700	0.77	0.19	8.8	37	-	1.26	0.20	0.97	25.18	0.57
L		0	2500	0.67	0.10	11.8	85	-	1.40	0.30	0.86	20.35	0.39
M		5	900	0.32	0.81	3.0	14	0.7369	0.94	0.13	1.56	38.22	0.86
N	PH 102	5	1700	0.32	0.54	7.0	22	0.2550	1.21	0.20	1.51	27.85	0.50
O		5	2500	0.22	0.49	9.1	31	0.0844	1.93	0.33	1.44	23.51	0.36
P		10	900	0.63	1.03	3.3	9	0.8323	0.76	0.09	1.59	37.89	0.82
Q		10	1700	0.48	0.67	6.1	17	0.4848	1.06	0.20	1.56	27.69	0.47
R		10	2500	0.63	0.37	7.5	21	0.3030	1.16	0.32	1.10	23.42	0.39

Crushing strength (CS). This was determined for 6 tablets using an Erweka TB24 (Germany) apparatus.

Friability (Fr). Weight loss through friability was determined for 10 tablets after 15 min in an Erweka TAP (Germany) apparatus at 25 r.p.m..

Disintegration time (DT). The disintegration time of 6 tablets was measured individually using distilled water as the attacking medium in an apparatus Turu Grau (Spain) fulfilling the USP XXI Ed. specifications.

Dissolution rate. The dissolution rate of prednisone was determined for 6 tablets as per the procedure established in the USP XXI Ed. using Dissolutest Prolabo (France) apparatus. The active principle dissolved in the attack medium was determined spectrophotometrically at 243 nm and the dissolution rate was characterized by means of the dissolution efficiency in 30 min (DE) (11).

Microstructural characterization. Micropore structure was defined by means of three tests:

Water penetration. The total volume of water penetrating a tablet in 120 s (VW) was determined, three times for the same formulation, using the apparatus described by Couvreur et al. (12).

Mercury intrusion porosimetry. A Micromeritics 9305 Pore Sizer (USA) with 3 ml penetrometer for solids was employed. Working pressures covered the range 0.6-25000 psi. The total porosity (TP) and the pore size distribution were determined three times for each formulation, the latter from the corresponding geometric mean and standard deviation (DG and σ_G), after fitting to a log-normal distribution (13).

Adsorption of nitrogen. Samples of the tablets corresponding to formulations manufactured at the upper and lower limits of the compression force were tested in a Micromeritics ASAP 2000 (USA) apparatus, after degassing them at 105° C and 10^{-3} mm Hg. Nitrogen adsorption was at 77º K and relative pressures from 0.01 to 0.98. The specific surface area of the samples was estimated from

$$s(m^2/g) = 4.37\ Vm\ (cm^3/g)$$

where Vm is the volume of nitrogen necessary to form a monolayer and can be calculated with the BET equation (14).

The nitrogen adsorption data were used to estimate the Polanyi adsorption potentials (Eo and Em) (15).

Experimental design and statistical analysis

The characteristics of the formulations studied (Table 1) followed a factorial design for three variables: variety of microcrystalline cellulose (characterised by its mean particle size), percentage of drug and maximum compression force; the first of these at two levels and the others, at three. Results were treated statistically by analysis of variance corresponding to the experimental design employed (16), which frequently gives many significant variables and interactions (17). The magnitude of the influences of the terms with the greatest contribution were obtained as regression equations by stepwise multiple regression using the BDMP.P2R (17) package. There were no replicate measurements for the parameters coefficient of variation of weight and weight loss by friability, hence ANOVA was not possible; the effects of the variables were assessed by introducing all the variables, both independently and as interactions, in the regression.

RESULTS AND DISCUSSION

The mean experimental values of the parameters for the different formulations are shown in Table 1. The corresponding ANOVAs (Table 2) show that many terms are significant to some extent. The influence, both independently and in interactions with other variables, of the variable variety of microcrystalline cellulose (expressed as mean particle size) is evident. There is, in effect, a difference in behaviour between the two excipients.

The low values obtained for the coefficient of variation of tablet weight suggest that the flowabilities of the two celluloses are suitable for the manufacturing conditions. Nonetheless, the regression equation for this parameter

$$CV\ (\%) = 1.62 - 1.09\ 10^{-2}\ V$$

$$R = 0.6065;\ p > 99\%$$

shows that the PH 102 variety gives better results. This is explained by the fact that this granular variety has a greater mean particle size than PH 101 (18). Nevertheless, the smaller value obtained for the correlation coefficient means that the equation has a smaller predictive value.

The regression equations for the parameters characterizing the mechanical properties, i.e. crushing strength and weight loss by friability,

$$CS\ (kg) = -5.06 + 4.30\ 10^{-2}\ V + 6.89\ 10^{-3}\ CF - 7.87\ 10^{-7}\ CF^2 + 1.50\ 10^{-2}\ D^2 - 1.91\ 10^{-3}\ V\ D - 1.40\ 10^{-6}\ V\ CF\ D$$

$$R = 0.9866;\ p > 99\%$$

TABLE 2

Summary of the results of analysis of variance for the different parameters.

	CS[a]	DT[b]	DE[a]	NW[b]	WE[b]	VW[b]	TP[b]	DG[b]
V	201.36*	441.93*	177.62*	13.52*	0.01	23.77*	16.69*	344.07*
CF	4029.20*	487.02*	1293.82*	319.42*	215.44*	154.02*	199.71*	34.85*
D	356.12*	327.03*	181.49*	0.97	4.67**	130.23*	13.95*	36.85*
CF^2	38.99*	4.21•	9.10*	0.19	2.71	0.87	0.14	9.01*
D^2	37.92*	55.77*	-	1.48	9.19*	120.58*	8.63*	0.01
V*CF	0.45	195.35*	0.48	4.36**	3.80	0.52	31.48*	2.54
V*D	104.42*	225.57*	0.09	10.34*	1.63	8.48*	12.55*	9.72*
CF*D	49.48*	155.33*	21.53*	1.99	3.89	0.15	12.11*	3.32
$V*CF^2$	9.88*	7.62*	30.57*	0.77	0.14	0.58	8.99*	3.16
$V*D^2$	2.27	8.22*	-	1.59	12.02	1.36	2.59	1.14
CF^2*D	0.07	12.63*	18.44*	0.00	0.04	19.12*	0.29	1.80
$CF*D^2$	0.47	19.55*	-	4.05	6.33**	27.19*	0.37	0.11
CF^2*D^2	2.81	3.07	-	0.02	5.40**	0.18	0.07	0.82
V*CF*D	39.37*	170.66*	0.67	0.11	2.82	1.25	0.00	0.06
$V*CF*D^2$	1.23	56.89*	-	0.15	0.00	0.84	2.42	0.12
$V*CF^2*D$	0.34	18.05*	2.84	3.26	3.68	1.63	3.44	0.80
$V*CF^2*D^2$	0.25	0.23	-	3.05	0.03	0.30	2.40	0.25

* *Significant at the $\alpha < 0.01$ level*
** *Significant at the $0.01 < \alpha < 0.05$ level*

[a] *1, 60 d.f.*
[b] *1, 37 d.f.*

$$Fr\ (\%) = 1.99\ 10^{-1} + 2.55\ 10^{-1}\ D - 1.03\ 10^{-4}\ CF\ D$$

$$R = 0.8096;\ p > 99\%$$

show different dependencies with respect to the variables. Whereas the crushing strength is strongly influenced by the variety of cellulose, friability does not figure in the regression equations for either variety. This might be explained, as can be deduced from Figure 1 showing the response surfaces corresponding to the two parameters, by the fact that the differences between the values of crushing strength for formulations containing little prednisone decrease and practically disappear as the proportion of drug is increased up to 10%. For the weight loss by friability, however, the values increase sharply when the proportion of active principle increases, which may hide the possible effect of the variety of cellulose.

The large influence of maximum compression force on the mechanical properties of the tablets was expected (19). Not expected, however, was that the deficiencies observed in these properties should get larger as the proportion of the drug is increased. This may be due to the degradation, revealed in another study (20), of the flow properties of the mixtures, which become more compressible as the amount of prednisone is increased. This behaviour is illustrated by the large weight loss by friability for formulations containing 10% prednisone, in particular those manufactured at low compression forces, which is probably as a result of the energy lost when the particles reorder during compression. The equations obtained for the parameters net work of compression and energy regained by elasticity,

$$NW\ (J) = 1.30\ 10^{-1} + 6.37\ 10^{-4}\ CF - 5.83\ 10^{-10}\ CF^2\ D^2$$

$$R = 0.8662;\ p > 99\%$$

$$WE\ (J) = -6.65\ 10^{-2} + 2.11\ 10^{-4}\ CF - 5.66\ 10^{-7}\ V\ CF$$

$$R = 0.9186;\ p > 99\%$$

support this hypothesis since, as the response surface shows (Fig. 2), increasing the proportion of prednisone in the formulations causes the first of these parameters to decrease, but there is no change in the elastic recuperation. Furthermore, the results obtained in the nitrogen adsorption tests (Table 3) show fragmentations of the particles do not occur during compression, since ANOVA showed no significant changes in the Polanyi adsorption potentials (Table 3) when the compression force is increased (15).

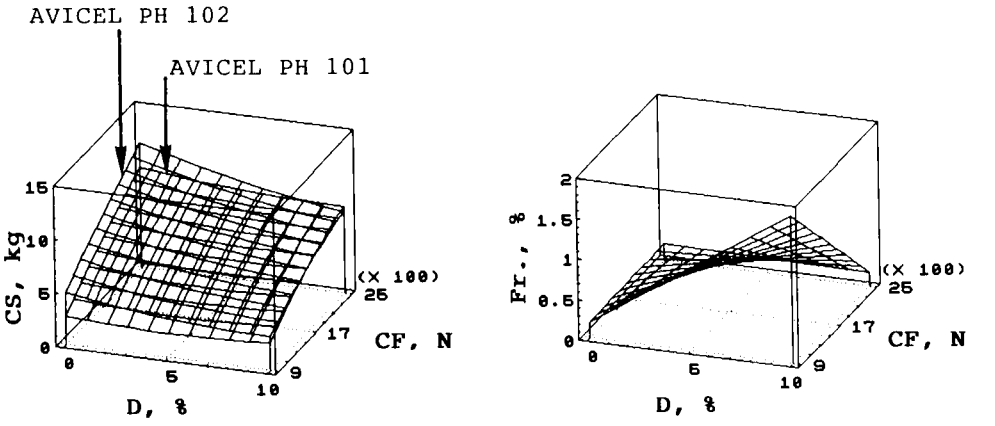

FIGURE 1

Response surfaces corresponding to the parameters crushing strength and loss of weight by friability for each of the varieties of microcrystalline cellulose.

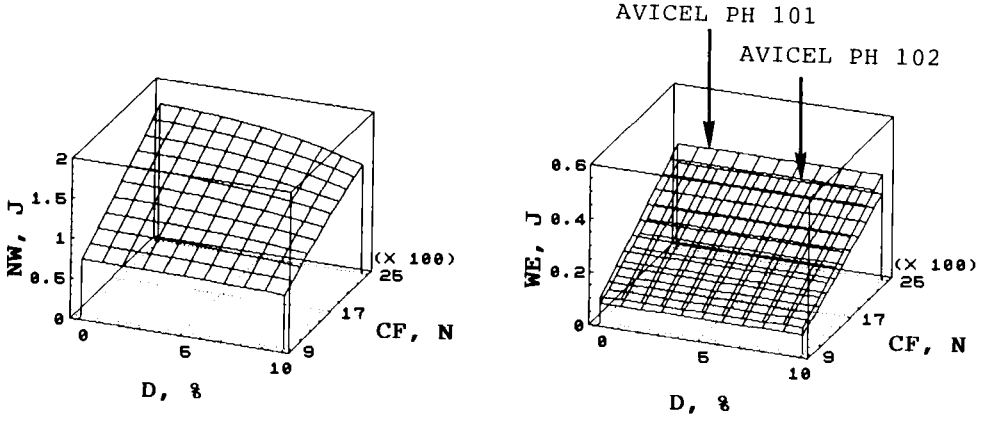

FIGURE 2

Response surfaces corresponding to the parameters net work of compression and energy recovered by elasticity.

TABLE 3

Mean values of the specific surface area and Polanyi adsorption potentials for the formulations described.

FORMULATION	S (m^2/g)	E_o (kJ/mol)	E_m (kJ/mol)	V_m (cm^3/g)
D	1.53	3.91	1.24	0.3517
F	1.29	4.14	1.25	0.3060
G	1.61	3.95	1.19	0.3705
I	1.49	4.02	1.18	0.3437
M	1.40	4.24	1.24	0.3212
O	1.32	4.01	1.29	0.3040
P	1.50	4.03	1.23	0.3416
R	1.45	4.00	1.24	0.3348

With regards the parameters that characterize the release of prednisone, the regression equations

$$DT\ (s) = -11.86 + 2.20\ 10^{-1}\ D^2 + 3.32\ 10^{-4}\ V\ CF - 3.00\ 10^{-5}\ V\ CF\ D$$

$$R = 0.9349;\ p > 99\%$$

$$DE = 1.58 - 3.51\ 10^{-3}\ V - 7.40\ 10^{-4}\ CF + 6.58\ 10^{-8}\ CF^2 + 2.06\ 10^{-5}\ CF\ D$$

$$R = 0.9679;\ p > 99\%$$

and the corresponding response surfaces (Fig. 3) show, again, the influence of the variety of microcrystalline cellulose. Formulations manufactured with PH 102 had longer disintegration times than those containing the variety with smaller particles. Nevertheless, in an analogous way to the crushing strength, these differences were less and almost went to zero in the formulations containing most prednisone. With respect to the dissolution rate of the active principle, the behaviour was also analogous. Dissolution efficiency in 30 min were greater for the formulations containing Avicel PH 101. Likewise, the influence of the compression force was very great at low drug proportions, and became weaker as more prednisone was used.

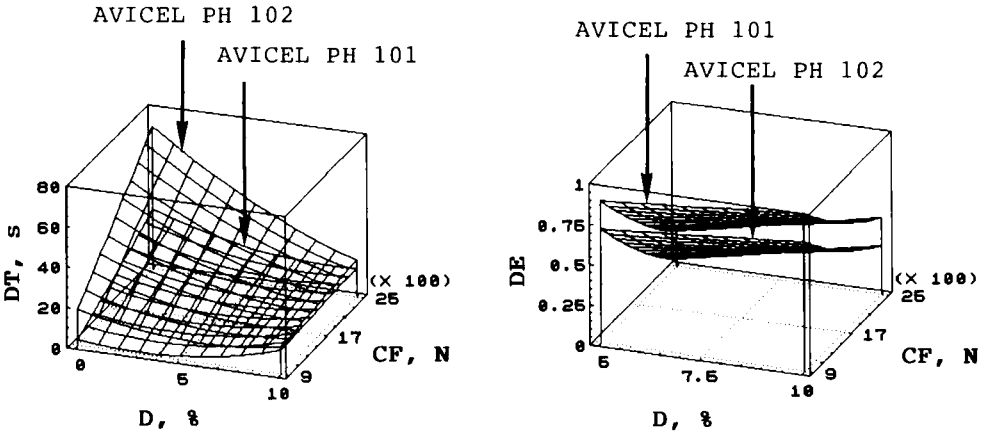

FIGURE 3

Response surfaces corresponding to the parameters disintegration time and dissolution efficiency in 30 min.

The regression equations corresponding to the parameters for the microporous structure of the tablets were

$$VW\ (ml/g) = 1.76 - 3.60\ 10^{-3}\ V - 2.03\ 10^{-4}\ CF + 1.06\ 10^{-1}\ D - 9.90\ 10^{-3}\ D^2 + 3.04\ 10^{-4}\ V\ D$$

$$R = 0.9100;\ p > 99\%$$

$$TP\ (\%) = 35.37 - 5.75\ 10^{-5}\ V\ CF + 1.01\ 10^{-2}\ V\ D - 3.06\ 10^{-4}\ CF\ D$$

$$R = 0.9640;\ p > 99\%$$

$$DG\ (\mu m) = 2.08 - 5.65\ 10^{-3}\ V - 7.53\ 10^{-4}\ CF - 4.52\ 10^{-2}\ D + 1.20\ 10^{-7}\ CF^2 + 3.69\ 10^{-4}\ V\ D$$

$$R = 0.9498;\ p > 99\%$$

The amount of water entering the structure of the tablets manufactured with the PH 102 variety was significantly less than those containing the other variety, but this difference decreased as the amount of prednisone in the formulations increased (Fig. 4). The mercury porosimetry studies revealed that the pore sizes fit a log-normal distribution (in Fig. 5 the distribution curves corresponding to some formulations which are indicated are given as an example). The degree of fit was good in all cases, the lowest values being an F

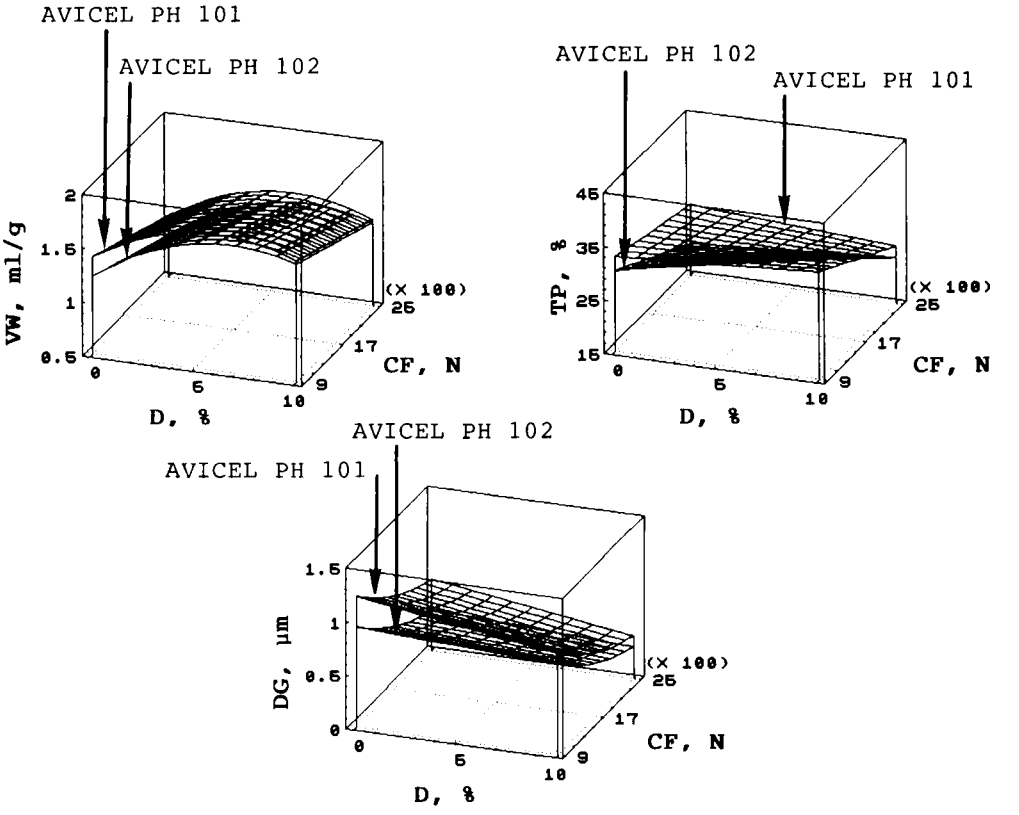

FIGURE 4

Response surfaces corresponding to the parameters volume of water penetrating tablet structure, total porosity and mean pore diameter.

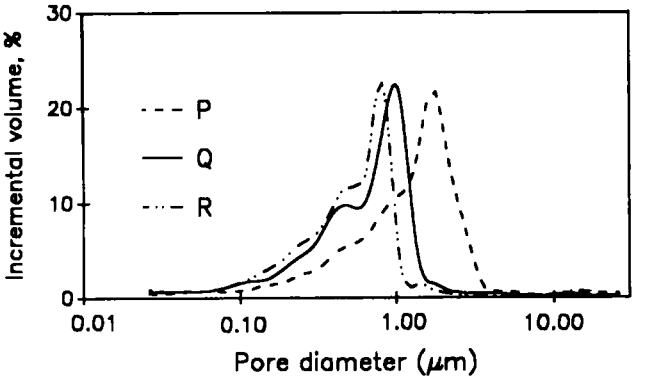

FIGURE 5

Pore size distribution curves for the formulations indicated

TABLE 4

Values of the mean tensile strength and degree of interaction between particles

FORMULATION	TENSILE STRENGTH (MPa)	DEGREE OF BONDING BETWEEN THE PARTICLES
A	0.55	
B	1.47	$5.4253\ 10^{-2}$
C	2.24	
D	0.49	
E	1.17	$4.8178\ 10^{-2}$
F	2.08	
G	0.47	
H	1.33	$4.9145\ 10^{-2}$
I	2.04	
J	0.89	
K	2.14	$7.8828\ 10^{-2}$
L	3.22	
M	0.63	
N	1.71	$5.9798\ 10^{-2}$
O	2.40	
P	0.74	
Q	1.53	$5.1671\ 10^{-2}$
R	1.97	

of the regression and correlation coefficient $F=569.24$ (with 1, 60 d.f.) and $r=-0.9466$. These results indicate, as shown by Zoglio and coworkers (21), the dominance of pores between particles. Furthermore, the response surfaces corresponding to mean pore diameter, estimated in terms of the log-normal fit, and the total porosity (Fig. 4) indicate these parameters take greater values for the tablets with Avicel PH 101 than for those containing Avicel PH 102. These differences also decrease as the proportion of prednisone increases.

In order to account for the dependence on the proportion of prednisone observed for the difference between the values of a property for tablets containing the two varieties of cellulose, the degree of bonding between the particles in the tablets was estimated by

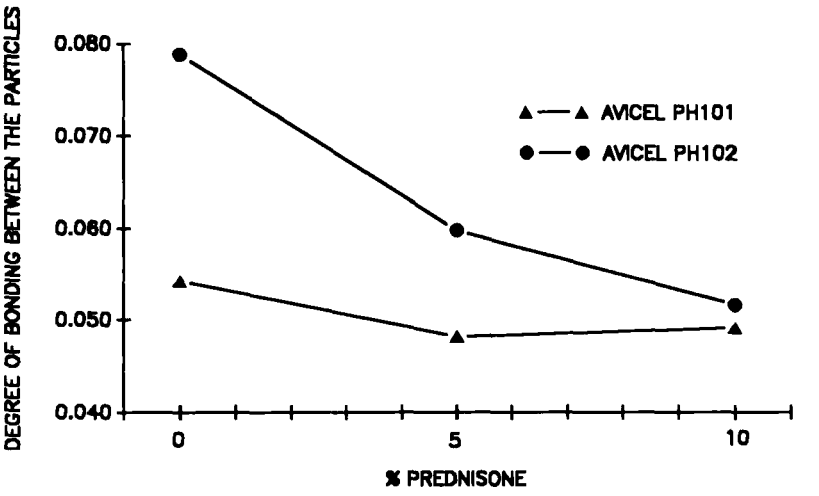

FIGURE 6

Relation between degree of interparticle bonding and percentage of prednisone for the two varieties of cellulose analysed.

means of the methodology proposed by Stanley-Wood et al. (15). The results obtained are shown with values of the mean tensile strength (Table 4).

When these are plotted against the percentage of prednisone (Fig. 6) it can be seen that the degree of interparticle interaction is greater in the formulations manufactured with the PH 102 variety, although increasing the proportion of prednisone leads to a sharp drop until, for 10% prednisone in the mixture, the value approaches that observed for formulations containing the PH 101 variety. The lesser sensitivity of Avicel PH 101 to the amount of prednisone is demonstrated by the less abrupt changes in the properties of the tablets when the proportion of drug is altered.

ACKNOWLEDGEMENTS

This work was supported by grant **FAR 88-0511 CICYT**. Ministerio de Educación y Ciencia. Spain.

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