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COMPARISON OF TWO VARIETIES OF MICROCRYSTALLINE CELLULOSE AS FILLER-BINDERS II. HYDROCHLOROTHIAZIDE TABLETS

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SUMMARY

In tests of direct-compression hydrochlorothiazide tablets prepared with either of two varieties of microcrystalline cellulose (Avicel PH 101 and Avicel PH 102), PH 102 tablets had better mechanical properties (owing to lower compressibility of mixtures and greater interparticle bonding), while PH 101 tablets released the active principle faster. These differences are related to observed differences in tablet micropore structure.

INTRODUCTION

In a previous study (1), we compared two varieties of microcrystalline cellulose (Avicel PH 101 and Avicel PH 102) in the formulation of direct-compression tablets of prednisone, a poorly hydrosoluble drug compressing mainly by plastic deformation. Cellulose variety was found markedly to affect the mechanical, microstructural and release properties of the tablets. We have now studied the same two excipients in tablets of hydrochlorothiazide, a drug that is likewise poorly hydrosoluble but is compressed principally by particle fragmentation (2).

MATERIALS AND METHODS

Active principle and excipients

Hydrochlorothiazide (lot 014, J. Escuder, Spain); mean particle size 56.4 μm (Coulter method).

Microcrystalline celluloses (Avicel PH 101 and Avicel PH 102, nominal mean particle sizes 50 μm and 100 μm respectively) and magnesium stearate as previously (1).

Formulations

Table 1 shows the characteristics defining the 18 formulations studied: variety of microcrystalline cellulose (V), percentage of hydrochlorothiazide (D) and maximum compression force (CF). Tablet preparation was as previously (1).

Rheological characterization of the mixtures

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 up to 20 min. These densities were used to calculate the compressibility (C) of mixtures (3).

Characterization of the compression process

Compression force-displacement cycles recorded for each formulation were used to calculate the parameters Net Work of Compression (NW) and Energy Loss Elasticity (WE) (1).

Characterization of the tablets

Tablet dimensions, cefficient of variation of weight (CV), crushing strength (CS), friability (Fr) and disintegration time (DT) were determined for each formulation as previously (1).

Dissolution efficiency at 30 min (DE) was determined using six tablets in a Prolabo (France) Dissolutest apparatus (USP XXI Ed.); drug concentration in samples was determined spectrophotometrically at 242 nm (4).

Tablet microstructure was characterised by total volume of water absorbed in 120 s

TABLE 1

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

Formulation	V	D %	CF N	CV %	Fr %	CS kg	DT s	DE	NW J	WE J	VW ml/g	TP %	DG m
A		0	900	0.48	0.19	3.0	13	-	0.78	0.12	0.88	31.45	1.21
B		0	1700	1.40	0.00	6.7	16	-	1.23	0.23	0.71	30.16	0.93
C		0	2500	0.97	0.00	9.1	17	-	1.70	0.47	0.66	28.36	0.74
D		5	900	0.35	0.53	3.4	16	0.8609	0.74	0.12	0.81	36.10	1.34
E	PH 101	5	1700	0.43	0.16	6.2	20	0.6334	1.34	0.24	0.69	35.59	0.86
F		5	2500	1.15	0.02	10.2	27	0.5037	1.64	0.32	0.65	26.15	0.58
G		10	900	0.48	0.74	2.9	9	0.8353	0.77	0.12	0.68	33.09	1.37
H		10	1700	0.48	0.18	6.4	16	0.7038	1.27	0.24	0.67	29.59	0.80
I		10	2500	0.58	0.04	9.5	19	0.5590	1.85	0.30	0.60	27.54	0.61
J		0	900	0.67	0.45	4.5	16	-	0.47	0.09	0.72	32.23	0.97
K		0	1700	0.77	0.19	8.8	37	-	1.26	0.20	0.54	25.18	0.57
L		0	2500	0.67	0.10	11.8	85	-	1.40	0.30	0.42	20.35	0.39
M		5	900	1.29	0.45	4.7	14	0.8567	0.69	0.10	0.66	36.08	0.83
N	PH 102	5	1700	1.09	0.38	8.1	28	0.4446	1.28	0.26	0.50	27.93	0.57
O		5	2500	1.14	0.24	10.8	55	0.1950	1.88	0.28	0.44	22.51	0.44
P		10	900	0.43	0.33	5.7	20	0.6854	0.65	0.09	0.57	32.26	0.75
Q		10	1700	0.37	0.29	8.9	34	0.2798	1.42	0.24	0.44	24.66	0.49
R		10	2500	0.29	0.27	11.2	62	0.1439	1.82	0.25	0.36	19.91	0.42

TABLE 2

Values of compressibility obtained for the mixtures estudied.

	AVICEL PH-101	AVICEL PH-102
HYDROCHLOROTHIAZIDE 0%	36.3	31.4
HYDROCHLOROTHIAZIDE 5%	35.3	30.9
HYDROCHLOROTHIAZIDE 10%	35.4	30.0
HYDROCHLOROTHIAZIDE 100%	45.01	

(VW), total porosity (TP), mean (DG) and standard deviation (σG) of log pore diameter, specific surface area (S) and the Polanyi adsorption potentials (E_0 and E_m) (1).

Experimental design and statistical analysis

By ANOVA and stepwise multiple linear regression (1)(5)(6) for the 2x2x3 design used.

RESULTS AND DISCUSSION

Analysis of variance showed that cellulose variety (V) significantly influenced all tablet properties (Table 1).

The small values of CV show that the flow properties of all formulations were suitable for the compression conditions used. The regression equation for CV

$$CV\ (\%) = 0.91 - 0.04\ D^2 \quad (R = 0.5389;\ p > 99\%)$$

and the compressibility values (Table 2) show that addition of the drug slightly improved these properties. Avicel PH 102 afforded better compressibilities than Avicel PH 101.

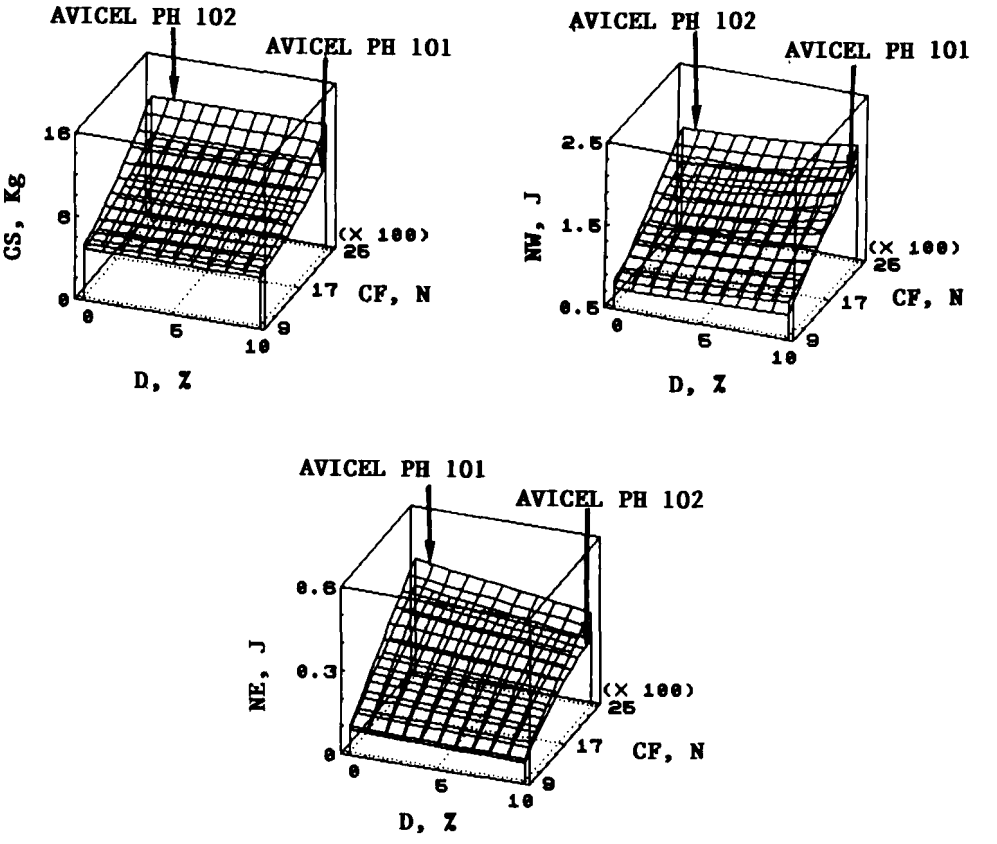

FIGURE 1
Response surfaces corresponding to the parameters crushing strength (CS), net work of compression (NW) and energy recovered by elasticity (WE).

Loss of weight due to friability was always below the customary 0.8% upper limit. The regression equation for crushing strength

$$CS\ (kg) = 4.05 + 0.13\ 10^{-7}\ V\ CF^2 \quad (R = 0.9154;\ p > 99\%)$$

show the influence of cellulose type but little or no effect of drug content, reflecting the slight improvement of compressibility upon addition of drug to microcrystalline cellulose excipients (7) (8). This is again reflected in the regression equations for net work of compression

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)
D	1.40	4.08	1.21
F	1.36	3.89	1.13
G	1.02	4.46	1.56
I	1.24	4.18	1.22
M	1.29	4.08	1.17
O	1.34	3.49	0.90
P	1.37	3.98	1.20
R	1.39	3.67	1.07

$$NW\ (J) = -0.26 + 0.76\ 10^{-2}\ V + 0.97\ 10^{-3}\ CF - 0.63\ 10^{-5}\ V\ CF + 0.13\ 10^{-7}\ V\ CF\ D^2$$

$$(R = 0.8618;\ p > 99\%)$$

and energy loss through elasticity

$$WE\ (J) = -0.13 + 0.26\ 10^{-3}\ CF - 0.31\ 10^{-9}\ V\ CF^2 - 0.14\ 10^{-8}\ CF^2\ D$$

$$(R = 0.9064;\ p > 99\%)$$

which show that drug addition slightly increased net work but had no appreciable effect on energy loss (Fig. 1).

The parameters measured by nitrogen absorption (Table 3) were not significantly affected by any of the independent variables, showing in particular that no appreciable fragmentation of hydrochlorothiazide particles took place. This is not the first report of such "protective" action by microcrystalline cellulose (9).

In keeping with the above results, interparticle bonding, measured as per Stanley-Wood et al. (10), was greater for PH 102 tablets and was not affected by drug addition (Fig. 2).

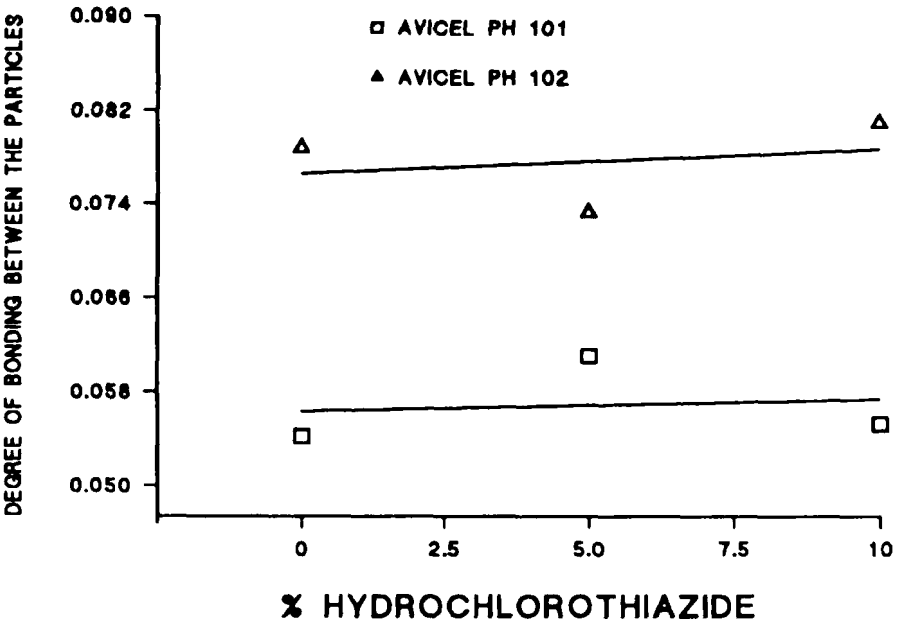

FIGURE 2
Relation between degree of interparticle interaction and percentage of hydrochlorothiazide for the two varieties of cellulose analysed.

The regression equation for disintegration time

$$DT\ (s) = -5.83 + 0.30\ 10^{-3}\ V\ CF - 0.18\ 10^{-4}\ V\ D\ CF + 0.14\ 10^{-5}\ V\ D^2\ CF$$

$$(R = 0.9225;\ p > 99\%)$$

shows that disintegration was slower for PH 102 tablets, and was speeded by drug addition (Fig. 3). Similarly, the equation for dissolution efficiency

$$DE = 0.64 + 0.01\ V + 0.04\ D - 0.88\ 10^{-5}\ V\ CF - 0.65\ 10^{-3}\ V\ D + 0.15\ 10^{-8}\ V\ CF^2$$

$$(R = 0.9525;\ p > 99\%)$$

shows slower release by PH 102 tablets, for which DE was more affected by maximum compression force and drug content than it was for PH 101 tablets (Fig. 3). In keeping with these results, the regression equation for VW

$$VW\ (ml/g) = 1.77 - 0.46\ 10^{-3}\ CF - 0.05\ D + 0.10\ 10^{-6}\ CF^2 + 0.42\ 10^{-4}\ CF\ D - 0.20\ 10^{-5}\ V\ CF - 0.23\ 10^{-6}\ V\ D\ CF \quad (R = 0.9295;\ p > 99\%)$$

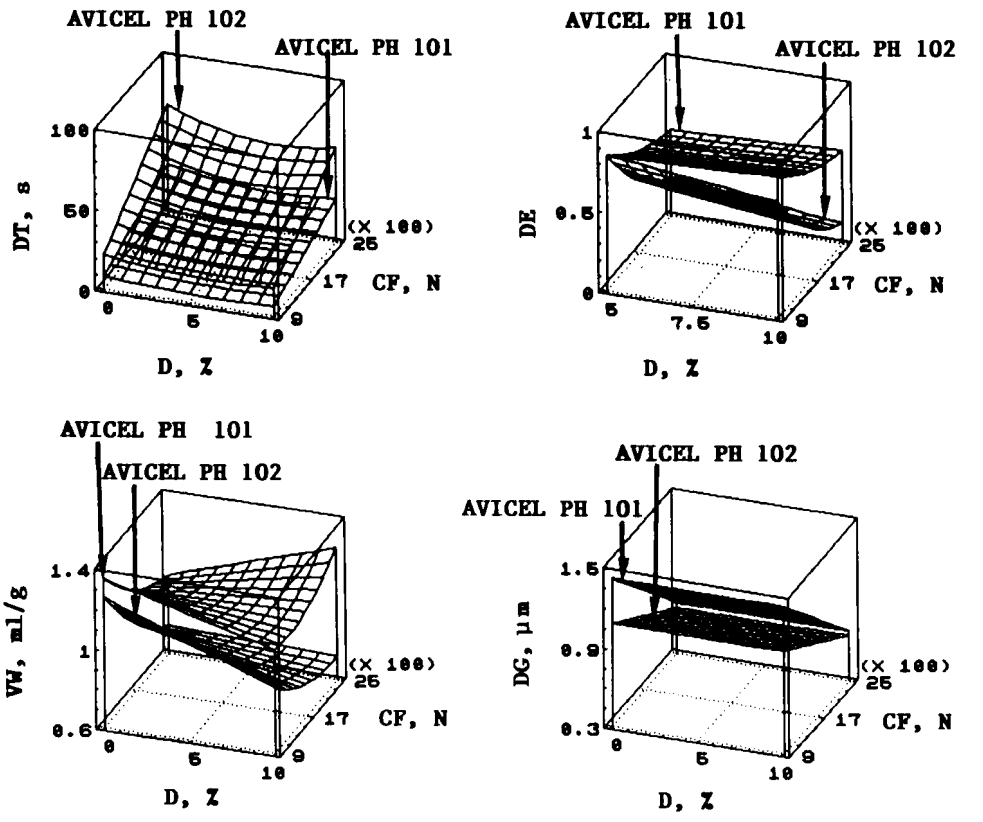

FIGURE 3
Response surfaces corresponding to the parameters disintegration time (DT), dissolution efficiency in 30 min (DE), volume of water penetrating tablet structure (VW) and mean pore diameter (DG).

shows that PH 102 tablets took up less water, and were more influenced in this respect by NW and D, than PH 101 tablets (Fig. 3).

Pore size, as measured by mercury intrusion porosimetry, exhibited log normal distributions, showing that the pores measured by this process are almost entirely interparticle spaces (11). The regression equation for mean pore diameter

$$DG\ (m) = 2.32 - 0.01\ V - 0.64\ 10^{-3}\ CF + 0.37\ 10^{-5}\ V\ CF \qquad (R = 0.9402;\ p > 99\%)$$

shows pore size to be larger for PH 101 tablets, and independent of drug content

(Fig. 3). The equation for total porosity

$$TP\ (\%) = 33.27 - 0.20\ 10^{-7}\ V\ CF^2 \qquad (R = 0.8090;\ p > 99\%)$$

likewise shows the PH 101 tablets to be the more porous; again, drug content had no effect. Their greater porosity may explain why drug release from PH 101 tablets was less affected by drug content than for PH 102 tablets.

Comparison of the present results with those of our previous study (1) shows that the behaviour of PH 101 tablets was very similar for both prednisone and hydrochlorothiazide as active principles, whereas the properties of PH 102 tablets were much more sensitive to prednisone content than to hydrochlorothiazide content. The differential behaviour of the PH 102 tablets may be attributed to prednisone particles being smaller than hydrochlorothiazide particles: the smaller particles mix with the microcellulose in an ordered fashion that hinders cellulose-cellulose hydrogen bonding (12), and the hindrance is greater for the larger cellulose particles (PH 102) than for the smaller (PH 101).

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