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RELATIONSHIPS BETWEEN FLOW PROPERTIES, COMPRESSION BEHAVIOUR AND MECHANICAL CHARACTERISTICS OF PREDNISONE-MICROCRYSTALLINE CELLULOSE TABLETS

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SUMMARY

This paper describes the effects on the flow properties, as well as the changes in the compression behaviour, of microcrystalline cellulose (Avicel PH 101) incorporated with prednisone together with the mechanical properties of compacts made by direct compression from mixtures of these components.

There is a gradual degradation of the flow properties of the mixtures with increase proportions of prednisone. At the same time there is a close correlation between the parameters chosen to characterise the flow properties of the mixtures (unconfined yield stress, major consolidation stress and flow factor) and the compression work which influence the mechanical properties (crushing strength and friability) of compacts manufactured at low uniaxial compression forces.

INTRODUCTION

Since the introduction, in the 1950's, of the first excipients for the production of tablets by direct compression, this technique has been a subject of interest; due to the many advantages it holds (1-3). The application of direct compaction on an industrial scale has been restricted because of certain important drawbacks (1, 4), the evasion of which has been overcome by altering existing excipients or fabricating new ones. The deterioration of the flow properties of excipients when relatively high proportions of drug are incorporated, is one of the most problematic issues at present because several tablet properties are affected. Furthermore, although there are many appraisals of the effects of the materials' flow properties on certain parameters, such as the uniformity in weight of the tablets (5-7), those describing their influence on the mechanical properties and the release of the active principle are uncommon.

This paper presents a study on the flow properties of a direct-compression excipient, microcrystalline cellulose, by incorporating prednisone into the powdered system and the effect this has on the compression behaviour of these mixtures and the mechanical properties of compacts obtained.

MATERIALS AND METHODS

Active principle and excipients

-Prednisone (lot 842-B, J. Escuder, Spain).

-Microcrystalline cellulose (Avicel PH 101, lot 852, C. Barcia, Spain).

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

Formulations

Six different formulations were prepared (Table 1) containing various proportion of prednisone and then compacted at a maximum uniaxial force of compression of 650 and 1300 N.

The materials were mixed in a Turbula T2C mixer for 15 mins at 30 r.p.m. The tablets were obtained by direct compression of the mixtures in a Korsch EKO excentric instrumentalised press (8), adjusted to produce tablets of 200 mg in weight for each formulation.

Table 1
Characteristics of the various powder mixtures and formulations studied.

Mixture	Composition (%)	Formulation	Maximum Compression Force (N)
A	Prednisone (0) Avicel PH 101 (99.5) Magnesium Stearate (0.5)	1	650
		2	1300
B	Prednisone (5) Avicel PH 101 (94.5) Magnesium Stearate (0.5)	3	650
		4	1300
C	Prednisone (10) Avicel PH 101 (89.5) Magnesium Stearate (0.5)	5	650
		6	1300

Rheological characterisation of the mixtures

Each mixture was subjected to the following tests:

-*Shear stress at failure*.- This was determined at different values of normal stress using a Jenike standard cell (9). The flow factor (ff) (10) parameter was chosen to characterise the flow properties of all mixtures and both non-formulated materials.

The flow factor was evaluated by the following procedure: two Mohrs semicircles were drawn tangentially onto the non-formulated or mixture yield locus. One Mohrs semicircle was drawn through the origin and touched the yield locus, the intersection on the abscissa gave the unconfined yield stress (fc). The other Mohrs semicircle, also tangential to the yield locus, was drawn to pass through the terminal point of the locus. The intersection of this semicircle with the abscissa gave the value of the maximum major consolidation normal stress (σ_1). The reciprocal of the slope of a graph of fc vs σ_1 can give an estimate of either the flow factor for each mixture or its flowability.

-*Packed density*.- A powder Hosokawa characteristic tester (Hosokawa Iron Works Ltd., Japan) 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 minutes. These tapped densities were used to calculate the compressibility (C) (11) of the powder.

Characterisation of the compression process

Each formulation was put through three separate cycles of compression; force-displacement and force-time profiles were defined by no less than 25 numerical values/cycle. The net compression work (N.W.) and the plasticity (P) were calculated from the force-displacement profile (12). The force-time cycles were characterised by the parameter area under the curve/maximum force of compression (AUCn), which, according to Chilamkurti et al, is an index for the materials' compressibility (13).

Characterisation of the tablets

The prepared tablets were subjected to the following tests:

-*Variation of weight* (V.C.)- This was obtained from the measured weights of thirty tablets and a statistical value obtained for the weight variation coefficient.

-*Crushing strength* (C.S.)- This mean parameter was determined from the crushing of ten tablets in a Erweka TB24 apparatus.

-*Friability* (Fr.)- The loss of weight due to friability was determined from ten tablets after 15 min in an Erweka TAP friabilater revolving at 20 r.p.m.

Experimental design and statistical analysis

With the aim of determining the rheological properties of the mixtures with different proportion of prednisone in microcrystalline cellulose mixtures an experimental design was chosen to observe three equally spaced criteria. The mixture composition and the fabrication compaction stress conditions were adapted to fit a 3x2 factorial experimental design. The factorially controlled variables then become the percentage of drug in the mixture (D) (three levels) and the maximum force of compression (F) (two levels).

It was thus possible to isolate the linear or quadratic terms of the effect of the proportion of drug (prednisone) in the excipient (microcrystalline cellulose) and see the behaviour of the tablet properties with varying compression force. To achieve this the experimental data were subjected to multiple linear regression (BMDP.P2R) (14) permitting the identification of the variables which have most influence over the observed effects.

RESULTS AND DISCUSSION

Graphs of unconfined yield stress (fc) vs the major consolidation stress (σ_1), obtained via the graphical method described, were plotted for each of the three mixtures (Fig. 1).

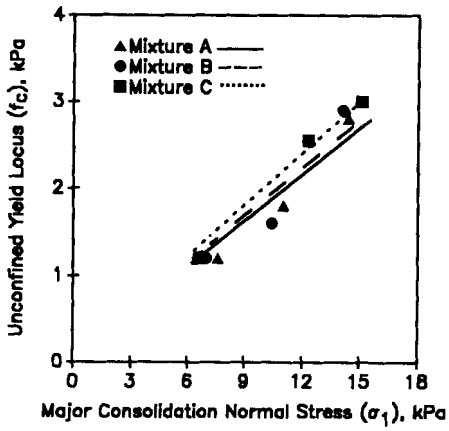

FIGURE 1
Unconfined yield stress vs. major consolidation normal stress for mixtures A, B and C (Table 1).

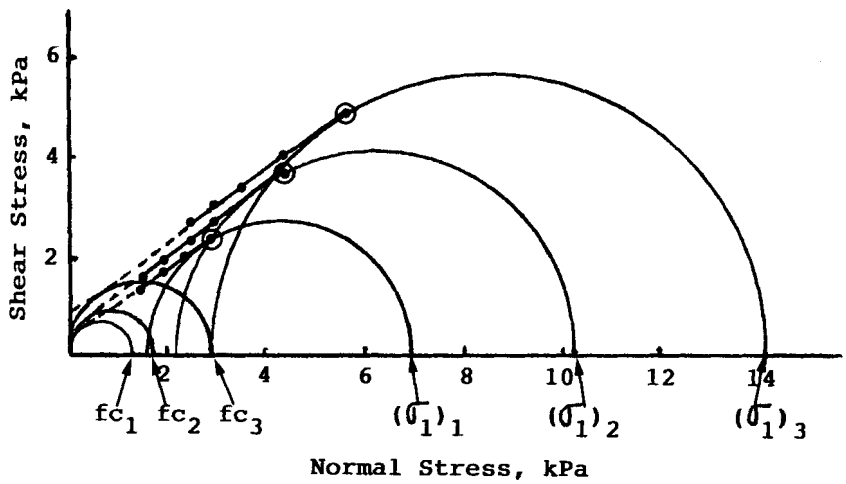

FIGURE 2
Mohrs circles obtained for the mixture B.

Table 2
Values of flow factor (ff) and compressibility (C) obtained for the mixtures studied.

Mixture	Flow Factor	Compressibility (%)
A	5.58	36.3
B	5.40	36.4
C	5.00	39.0

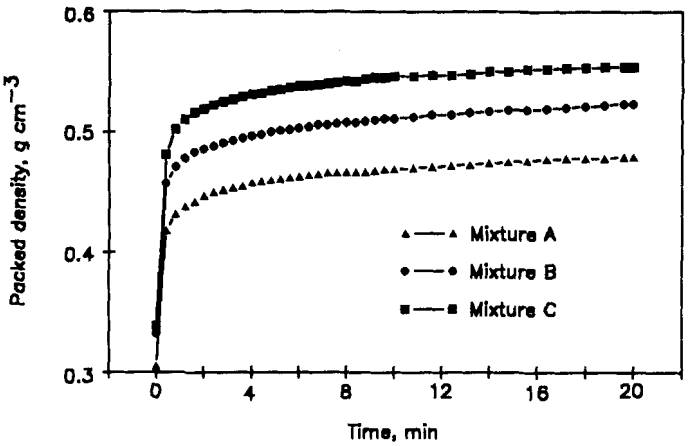

FIGURE 3
Packed densities at different stages of compacting for mixtures A, B and C (Table 1)

The yield loci and graphical evaluation of the unconfined shear stress (fc) and major consolidation stress (σ_1) for simplicity is only shown for mixture B (Figure 2). The calculated flow factors of the mixtures are given in Table 2. The apparent densities at different stages of compacting (Figure 3) were used to calculate the compressibilities of the mixtures (Table 2).

The results show that all the mixtures have acceptable flow properties (10) that surpass those of microcrystalline cellulose (Avicel PH 101), whose separate rheological properties have been studied here and by others (15). Values of 3.80 and 39.4% were obtained for the flow factor and compressibility respectively. An improvement in these properties was seen when 0.5% w/w of magnesium stearate was included in the mixture. If mixture A (no prednisone) is taken as a reference it can be seen that the incorporation of prednisone into the mixture expressed as percentage (D) causes a deterioration in flow properties. This effect can be mathematically expressed by the regression equations:

$$ff = 5.562 - 5.677\ 10^{-3}\ D^2$$
$$(R^2 = 0.9921;\ p>0.95)$$
$$C\ (\%) = 36.05 + 2.86\ 10^{-2}\ D^2$$
$$(R^2 = 0.9329;\ p>0.95)$$

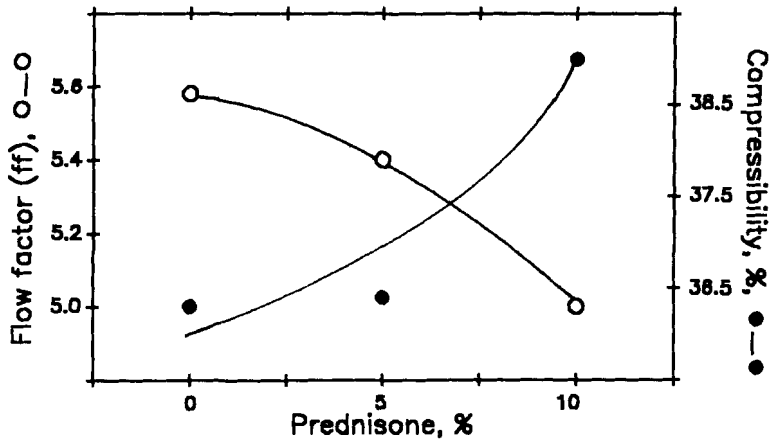

FIGURE 4
Effect of the incorporation of prednisone on flow factor and compressibility.

It can be seen that introduction of the active principle (prednisone) causes a decrease in the flow factor and an increase in the compressibility (Figure 4). This agrees with the work of Jenike (10) and Carr (16) who proposed that this was evidence of a greater cohesivity in the mixtures.

The mean values of the parameters chosen to define the response of the mixtures at different compression conditions (Table 3) were also subjected to a regression analysis to give:

$$AUCn\ (ms) = 62.65 - 3.222\ 10^{-3}\ F + 1.770\ 10^{-4}\ F\ D - 7.200\ 10^{-5}\ F\ D^2$$
$$(R^2 = 0.9986;\ p>0.99)$$

$$N.W.\ (J) = -0.14 + 1.195\ 10^{-3}\ F - 2.282\ 10^{-6}\ F\ D^2$$
$$(R^2 = 0.9969;\ p>0.99)$$

$$P\ (\%) = 79.25 + 7.104\ 10^{-3}\ F - 6.693\ 10^{-1}\ D + 4.400\ 10^{-5}\ F\ D^2$$
$$(R^2 = 0.9988;\ p>0.99)$$

These correlations were subsequently used to construct the response surfaces shown in Figures 5, 6 and 7. the correlations between AUCn, N.W. and P with the factorially controlled variables of D and F make it possible to determine the effects of the

Table 3
Mean values obtained for the parameters mentioned.

Formulation	AUCn (ms)	N.W. (J)	Plasticity (%)
1	60.7	0.64	83.9
2	58.4	1.43	88.4
3	59.9	0.58	81.2
4	57.4	1.33	86.7
5	57.1	0.51	80.0
6	51.5	1.11	87.5

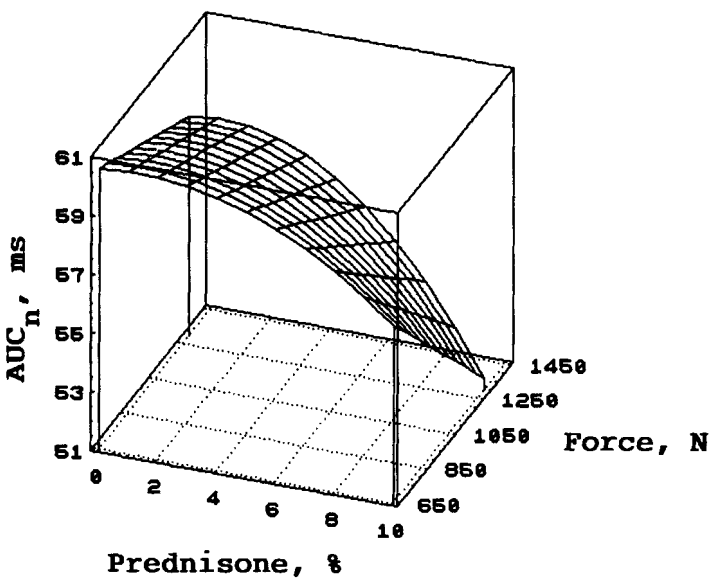

FIGURE 5
Response surface corresponding to the AUCn parameter.

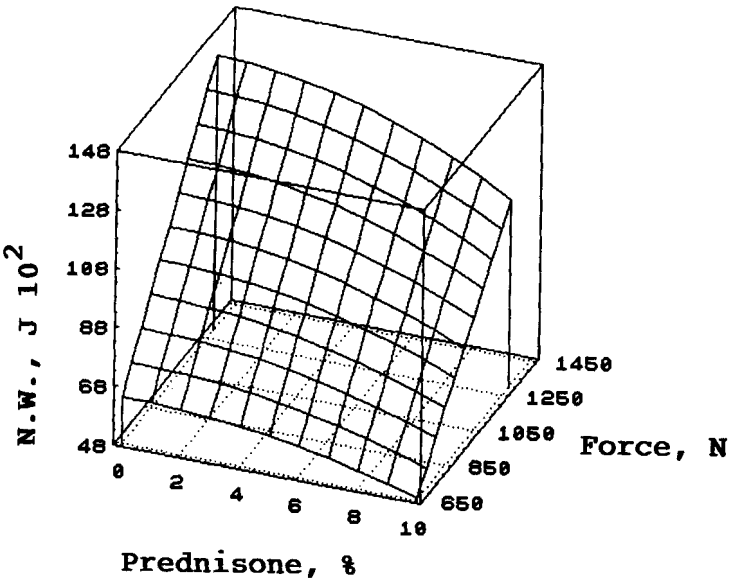

FIGURE 6
Response surface corresponding to the net work parameter.

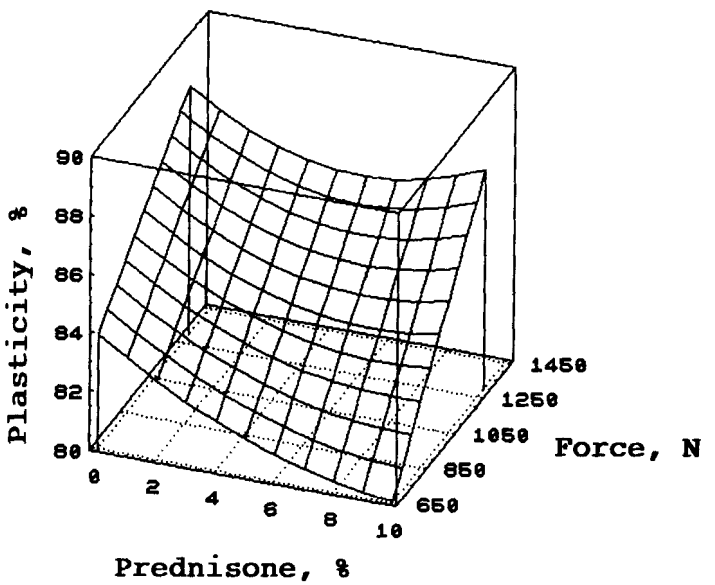

FIGURE 7
Response surface corresponding to plasticity.

Table 4
Mean values obtained for the parameters mentioned.

Formulation	V.C. (%)	C.S. (kg)	Fr. (%)
1	0.70	3.9	0.11
2	0.72	6.7	0.01
3	0.73	3.2	0.61
4	0.47	5.8	0.09
5	0.71	2.5	1.11
6	0.73	5.2	0.04

controlled variables over two of the most important aspects characterising the response of these materials to compression; i.e., compressibility and plasticity. The index for the first of these was taken as the parameter proposed by Chilamkurti et al. (13). Analysis of the corresponding response curve (Figure 5) reveals that AUCn decreases slightly as the mixtures become richer in prednisone, which implies an increase in the compressibility of the mixtures, that is, higher cohesivity, as the proportion of prednisone increases.

The plasticity of these mixtures (Table 3) is seen to decrease slightly when more prednisone is present (Figure 7) (3-4% in the worst case). This is to be expected since it is known that Avicel PH 101 and prednisone compress principally by plastic deformation (17). This implies that the sharp decrease seen in the Net Compression Work (Figure 6) is not due to an intense elastic component in the mixtures, but due to a greater energy loss through the reordering of particles. This energy loss occurs as a consequence of the increase in the cohesivity of the mixtures when there is a high proportion of prednisone present.

When the mean values of the data in Table 4 were subjected to regression analysis using the factorially controlled variables D and F the following mathematically correlations was obtained:

V.C. (%) = 0.68

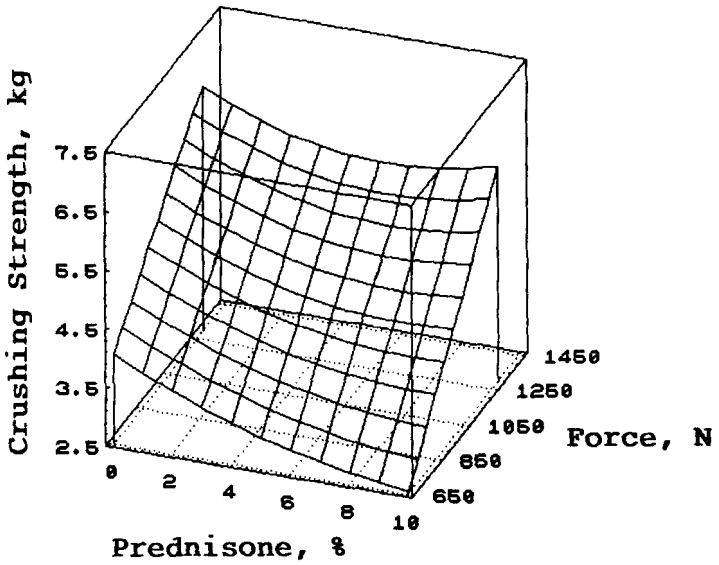

FIGURE 8
Response surface correponding to crushing strength.

$$C.S.\ (kg) = 1.402 + 4.038\ 10^{-3}\ F - 2.450\ 10^{-1}\ D + 1.500\ 10^{-5}\ F\ D^2$$
$$(R^2 = 0.9906;\ p > 0.99)$$
$$Fr.\ (\%) = 7.083\ 10^{-2} + 2.111\ 10^{-1}\ D - 1.640\ 10^{-4}\ F\ D$$
$$(R^2 = 0.9889;\ p > 0.99)$$

The correlations can then be used to give two tridimensional response surfaces as shown in Figures 8 and 9.

It is useful to observe the small change in the magnitude of the coefficient of variation of weight (V.C.) in terms of the other variables analysed. This underlines the easy flow properties possessed by the mixtures. In contrast, the mechanical properties of compacted mixtures diminish considerably as the proportion of prednisone in the mixture increases, with the exception of the friability at high compression forces, where this behaviour is weak.

Lastly, the high multiple correlation coefficient values obtained throughout lend a notable predictive capacity to the regression-fitted equations, making the relations

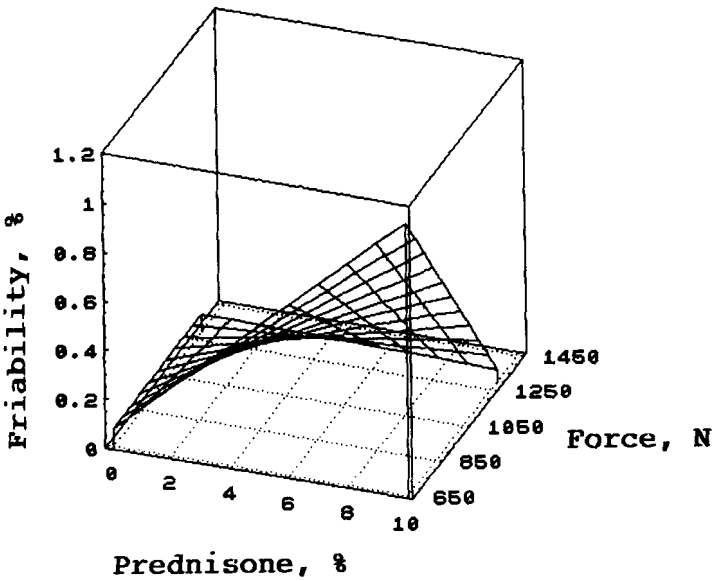

FIGURE 9
Response surface corresponding to friability.

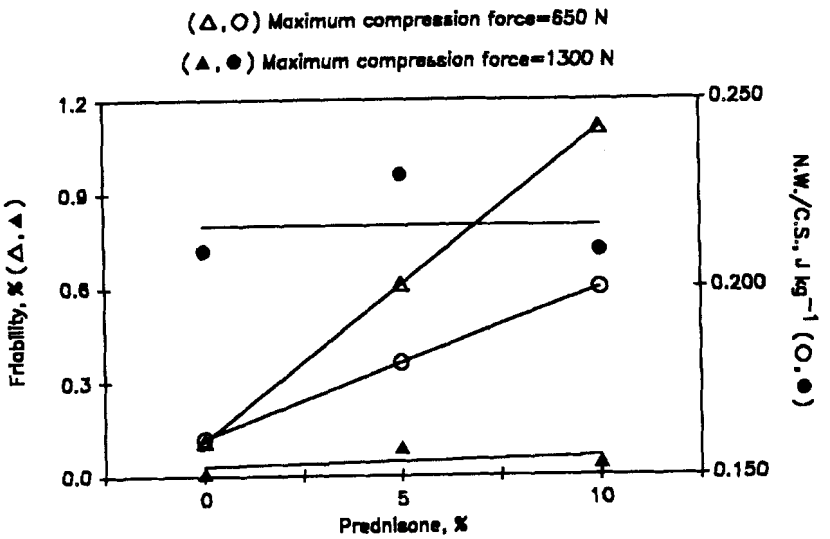

FIGURE 10
Energy incorporated per unit of crushing strength and friability of the tablets vs. percentage of prednisone in the mixtures.

between the chosen parameters strong. In this way, it is observed that, in accordance with Seberg's method (18), there is a close correlation between the two parameters characterising the mixtures' flow properties and the net work done, at the same maximum force of compression. The importance of the net compression work can be seen when the mechanical properties of the tablets are analysed. Figure 10 shows the energy incorporated per unit of crushing strength (N.W./C.S.) and the friability of the tablets (Fr.) versus the percentage of drug (D) in the mixtures. This indicated that the mechanical proporties of the tablets degrade in the presence of prednisone only when the compression force applied is low. This corresponds with a large loss energy seen by the reordering of particles and is a consequence of the increase in cohesivity of the mixtures.

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