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RESEARCH PAPER

Effect of Explotab® on the Tabletability of a Poorly Soluble Drug

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ABSTRACT

The efficiency of a superdisintegrant (Explotab®) in a direct-compression formulation containing a poorly water soluble drug (albumin tanate) at high dosage was investigated. An experimental design with two variables, applied pressure and concentration of Explotab, enabled its effects on the tableting and the mechanical properties of the final tablets to be determined. Differential scanning calorimetry was performed to study the interactions between drug and excipients. No incompatibility was found between drug–excipient mixtures prepared in the proportion 1:1 and in the corresponding formulation at room temperature and after 3 weeks at 50°C. The concentration of Explotab has a positive effect on flow properties. Also, the effect of applied pressure and disintegrant content was found to be significant on all compressional parameters. At low applied pressures, the breaking strength was independent on Explotab concentration. However, at higher applied pressures, the maximum densification obtained with 10% Explotab produced a limited breaking strength lower than that at 0% concentration. The response surface shows a certain level of Explotab, around 7%, at which the disintegration time was the shortest. At this level, the surface response was independent of the applied pressure. In our study, the experimental design was a valuable tool used to establish the optimum manufacturing conditions.

INTRODUCTION

Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release, mainly with high drug concentrations (1). In recent years, some new materials, called superdisintegrants, have been developed to improve the disintegration process. Sodium starch glycolate is the sodium salt of a relatively low substituted carboxymethylether of potato starch and is prepared by both crosslinking and substitution of potato starch. It is a widely used superdisintegrant in tablets prepared by both direct compression (2,3) and wet granulation (2,4). The superdisintegrant is currently marketed by two companies under the names Explotab® (Mendell) and Primojel® (Avebe). Several studies have shown that these two products behave differently and have concluded that this could be due to differences in the degree of molecular substitution arising from different manufacturing procedures (5,6).

Bolhuis et al. (7) compared the disintegration efficiency of sodium starch glycolates prepared from seven different native starches. All of the sodium starch glycolates tested had a high swelling capacity, but the rate of water uptake into the disintegrant particles varied from high for sodium potato starch glycolate to low for sodium rice starch glycolate.

Most of the studies that compared disintegrants and Explotab determined that Explotab had better disintegrating properties than others (8,9). Visavarungroj and Remon (9) found a progressive increase in disintegration time for different starches by increasing the tablet hardness. However, this phenomenon was not seen by these authors for some superdisintegrants, including Explotab. Baie et al. (10) showed for some modified tapioca starches, shorter disintegration times compared with those of Explotab at all concentrations and compaction forces used.

Gordon et al. (11) showed that aging affects the dissolution efficiency of tablets containing Explotab; this affect was more pronounced when Ac-di-sol® was used as disintegrant. Lerk et al. (12) found that the dissolution of prednisone from tablets containing sodium starch glycolate was independent of mixing with magnesium stearate and the compression force applied.

Johnson et al. (13) indicated that highly soluble and/or hygroscopic ingredients in tablets produced by wet granulation decreased the effectiveness of Explotab in promoting in vitro dissolution.

With the purpose to extend the use of this superdisintegrant, we studied Explotab in a direct-compression formulation containing a poorly soluble drug at high dosage in order to determine its effects on the tableting and mechanical properties of the final tablets.

Albumin tanate, which precipitates the proteins of intestinal mucous membrane and creates a protective barrier, was used as model drug. Albumin tanate is a poorly soluble drug and its bioavailability is more likely a result of the disintegration process.

MATERIALS AND METHODS

The sample tablet included the following ingredients: (*a*) albumin tanate (Kirsch Pharm, Spain, batch 63059); (*b*) microcrystalline cellulose as filler (Mingtai® M102, Isisa, Spain, batch 70821); (*c*) sodium starch glycolate (Explotab, Julia-Parrera, Spain, batch 123); (*d*) colloidal silica as glidant (Syloid®, Grace, Germany, batch AI-1), and (*e*) stearic acid as lubricant (Estearina® L2SH, José Escuder, Spain, batch 106). Powders were stored under controlled temperature (20°C) and relative humidity (RH 40%) conditions.

To study the interactions between drug and excipients, differential scanning calorimetry (DSC) was used. Thermograms were obtained for drug, filler, and Explotab. Also, two drug–excipient mixtures were prepared in the proportion 1:1 and in the corresponding formulation. Both mixtures were analyzed at room temperature and after 3 weeks at 50°C. DSC was performed on a DSC-7 (Perkin-Elmer, Norwalk, CT) instrument. All DSC runs, with samples as received and stored under conditions mentioned, were performed under an atmosphere of dry nitrogen (flow 23 ml/min), using the heating rate of 5°C/min. Powder samples of 1–3 mg in weight were crimped in perforated 50-µl aluminum pans.

Albumin tanate (71%), filler, and Explotab (0, 5, or 10% w/w) were mixed for 15 min in a plastic vessel in an asymmetric double-cone mixer (Retsch, Haan, Germany) at 48 rpm. After the addition of Syloid (0.1% w/w) and stearic acid (1% w/w), the mixing procedure was continued for 5 min. The final weight of tablets was 400 mg.

The powder flow was measured with an integrated system of data acquisition for the measurement of flow characteristics (14). The methodology used for determining the static repose angle and compressibility on tamping has been described in detail in earlier studies (15,16).

The compression characteristics of the powders were investigated by using an instrumented single-punch tablet machine (Bonals, model AMT 300, Barcelona, Spain)

with HBM YL6 strain gauges (HBM, Darmstadt, Germany) connected to dynamic amplifiers (NEC Sanei, Tokyo, Japan) and inductive displacement transducers (HBM) (17). Powder (400 mg) was manually filled into the die (12 mm). Tablets were prepared at three applied pressures (100, 200, and 300 MPa) to study compression properties of the mixtures. Also, to study tablet properties, the mixtures were tableted in the same single-punch machine running at 30 cycles/min and equipped with a forced feeding system.

The physical tests of tablets were performed according to European Pharmacopoeia II. The weight uniformity of the tablets was determined using model AE 100 analytical balance (Mettler Instruments, Greinfesee, Switzerland). The weight data from the tablets were analyzed for sample mean, standard deviation, and coefficient of variation. Friability was calculated from the weight loss of tablets tumbled at 100 revolutions in model TA-3 (Erweka, Heusenstamm, Germany) friability tester. Disintegration testing was performed at 37°C in HCl 0.1 N medium using model ZT-3 (Erweka) without disks.

Experimental Design and Statistical Analysis

The composition and elaboration conditions of the different formulations define a factorial design for two variables—maximum applied pressure during compression (P) and percentage of Explotab (D)—at three levels (formulations A, B, and C corresponding to 0, 5, and 10% of Explotab; formulations 1, 2 and 3 corresponding to 100, 200, and 300 MPa). Results were analyzed by ANOVA in order to select significant variables responsible for the changes observed. The quantification of the influence of these variables and interactions was obtained as regression equations by stepwise multiple regression.

RESULTS AND DISCUSSION

Table 1 shows the results for the flow parameters of the formulations with 0, 5, and 10% of Explotab. Although formulations did not show free flow by direct parameters, the addition of 10% of the disintegrant (formulation C) significally improved the results of indirect parameters (Haussner Index, percent compressibility and $V_{10} - V_{500}$) ($p < 0.05$). The spherical shape of the particles of the superdisintegrant could explain these results.

Although there are different methods to study the interaction between drug and excipients, DSC is the method of choice (18–20). Albumin tanate shows a characteristics peak at 195°C (195.26 ± 0.06) and Explotab shows a peak at 170°C (170.48 ± 3.7). From Table 2, we can conclude that the excipients are compatible with the drug.

The mean compression parameters for the different formulations are shown in Table 3. Table 4 shows the results of the statistical analysis of the independent variables (concentration and applied pressure) that can affect compression parameters and tablet properties. The effect of applied pressure and disintegrant content was found to be significant on all compressional parameters.

The response surface obtained for the lubrication coefficient shows the quadratic effect of the disintegrant on this parameter, mainly at low pressures. Applied pressure, as expected, improved the force transmission (21).

$$R = 0.922 - 0.00053P - 0.00095D^2 + 1.35E-6P^2 + 3.17E-6D^2P \qquad r = 0.862$$

In relation with the maximum ejection force (EF_{max}), the results show that all formulations carry out the supports proposed by Bolhuis and Lerk (22), with a value lower than 750 N. The following equation, fitted using

Table 1

Static Repose Angle (θ), Compressibility on Tamping (d_0, d_{500}, V_{10}–V_{500}), Haussner Index (IH), Percent Compressibility (%C), and True Density Parameters with Standard Deviations (SD) of the Formulations with 0, 5, and 10% of Explotab

Formulation	θ (°)	d_0 (g/cm³)	d_{500} (g/cm³)	V_{10}–V_{500} (ml)	IH	%C	d_{true} (g/cm³)
A: 0%	47.0	0.43	0.57	43.0	1.25	19.8	1.30
	(1.3)	(0.00)	(0.00)	(3.6)	(0.02)	(1.3)	(0.10)
B: 5%	48.5	0.43	0.60	46.0	1.28	21.6	1.33
	(1.0)	(0.00)	(0.01)	(4.3)	(0.03)	(2.1)	(0.04)
C: 10%	48.2	0.45	0.59	34.3	1.20	16.8	1.35
	(2.3)	(0.00)	(0.00)	(2.3)	(0.01)	(0.9)	(0.04)

Table 2

Characteristic Peaks and Standard Deviations (SD) Obtained with the DSC Analysis for Drug (Tanate), Filler (Mingtai M102), Superdisintegrant (Explotab), and Drug–Excipient Mixtures at Room Temperature and After 3 Weeks at 50°C

	Directly		3 Weeks 50°C	
	Test 1	Test 2	Test 1	Test 2
Tanate	195.22 (1.40)	195.30 (1.59)	192.46 (0.74)	194.55 (0.65)
Explotab	170.75 (11.22)	170.22 (11.93)	174.33 (10.03)	174.34 (8.37)
Tanate-M102 1:1	195.26 (0.52)	195.36 (0.57)	193.90 (0.53)	193.20 (0.37)
Tanate-M102 5:2	194.93 (0.56)	195.73 (0.69)	193.90 (0.63)	194.00 (0.69)
Tanate-Explotab 1:1	170.17 (3.25)	170.40 (3.40)	171.36 (3.36)	171.55 (3.03)
	194.13 (0.11)	195.32 (0.38)	193.10 (0.24)	192.00 (0.03)
Tanate-Explotab 9:1	194.64 (0.77)	196.24 (0.82)	193.30 (0.92)	193.50 (0.95)

stepwise multiple linear regression, quantifies the effect of the variables under study.

$$EF_{max}\ (N) = 7.857 + 29.600D + 2.387P - 0.358DP + 1.313D^2 - 0.004P^2 + 0.00069DP^2$$
$$r = 0.527$$

Table 3

Compression Parameters and Standard Deviations (SD) for the Different Formulations (A, B, and C Corresponding to 0, 5, 10% Explotab; 1, 2, and 3 Corresponding to 100, 200, and 300 MPa): Lubrication Coefficient (R), Maximum Ejection Force (EF_{max}), Plasticity (%P), and Apparent Net Work (W_{AN})

	R	EF_{max} (N)	$\%P$	W_{AN} (J)
A1	0.891	211.78	85.48	8.38
	(0.002)	(0.00)	(1.13)	(0.36)
A2	0.863	282.37	82.53	13.17
	(0.004)	(12.87)	(2.01)	(0.14)
A3	0.888	341.82	72.12	15.29
	(0.007)	(25.74)	(0.44)	(0.26)
B1	0.860	219.21	93.02	8.90
	(0.002)	(11.60)	(0.84)	(0.06)
B2	0.866	319.53	84.33	14.87
	(0.006)	(12.87)	(0.82)	(0.42)
B3	0.886	245.22	75.32	17.71
	(0.007)	(22.29)	(1.61)	(0.18)
C1	0.819	349.25	88.39	8.51
	(0.016)	(36.25)	(1.12)	(0.16)
C2	0.844	267.51	83.48	14.49
	(0.009)	(0.00)	(2.13)	(0.65)
C3	0.883	312.09	72.01	15.78
	(0.003)	(22.29)	(0.56)	(0.25)

The surface response (Fig. 1) shows that formulations with higher Explotab content are less sensitive to the variation of ejection force with applied pressure. This supports the results found by Muñoz et al. (23) for maltodextrins. The presence of a limit of plastic deformation (24) at a pressure scarcely lower than 300 MPa could explain the independent response of superdisintegrant concentration observed at these conditions.

The following equation was obtained for the apparent net work (W_{AN}):

$$W_{AN}\ (J) = 1.885 - 0.405D + 0.073P + 0.0078DP - 8.3E-5P^2 - 1.5E-5DP^2 - 2.16E-4D^2P$$
$$r = 0.992$$

The surface response based on this equation (Fig. 2) shows that, although the concentration of disintegrant has an insignificant effect on the apparent net work, this

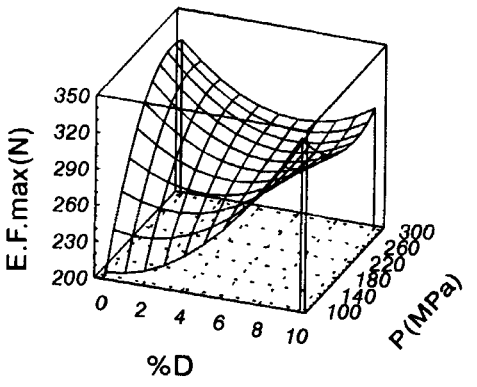

Figure 1. Surface response corresponding to maximum ejection force.

Table 4

F-Snedecor Values of the ANOVA of Each Parameter: Lubrication Coefficient (R), Maximum Ejection Force (EF_{max}), Plasticity (%P), Apparent Net Work (W_{AN}), Variation Coefficient (VC), Breaking Strength (BS), Friability (Fr), and Disintegration Time (DT)

Variation Source	% Disintegrant (D)	Applied Pressure (P)	$D \times P$
R	43.7**	44.3**	18.1**
EF_{max}	14.1**	10.0*	28.8**
$\%P$	23.8**	332.9**	4.3*
W_{AN}	33.4**	1418.9**	9.6**
VC	11413.8**	2490.1**	5401.3**
BS	30.3**	764.5**	11.7**
Fr	192218.1**	999999.9**	156453.8**
DT	11636.5**	1597.6**	1603.3**

**Statistically significant for $\alpha < 0.01$.
*Statistically significant for $\alpha < 0.05$.

parameter has a lineal increase when applied pressure is increased to reach the deformation limit of the particles (25). This pressure was lower when the concentration of Explotab was 10%.

The plasticity values were calculated from the following relation (26):

$$\%P = \frac{W_{AN}}{W_{AN} + W_{EXP}} \times 100$$

where W_{EXP} is the expansion work, and W_{AN} is the apparent net work, and they are between 72 and 93%. Although these values demonstrated a low expansion, they were higher than for tablets compressed from the plain filler (27).

The equation fit using multiple stepwise regression was:

$$\%P = 85.436 + 2.984D + 0.029P - 0.007DP - 0.256D^2 - 0.00024P^2 + 0.000567D^2P$$
$$r = 0.954$$

The surface response based on this equation (Fig. 3) shows a complex response to Explotab concentration, probably because of calculation of plasticity, that includes friction and expansion work (28,29). However, Velasco et al. (8) showed an improved plasticity with the addition of disintegrant, especially with Explotab, in calcium phosphate tablets. In this case, an additional effect of the disintegrant overcoming friction between particles of filler and die wall could assist expansion during compression.

The influence of the disintegrant on weight uniformity, thickness, friability, and disintegration is shown in Table 5.

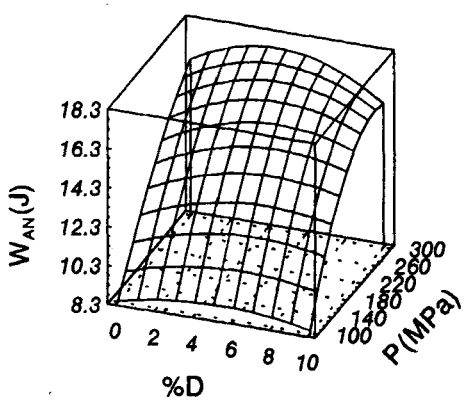

Figure 2. Surface response corresponding to the apparent net work parameter.

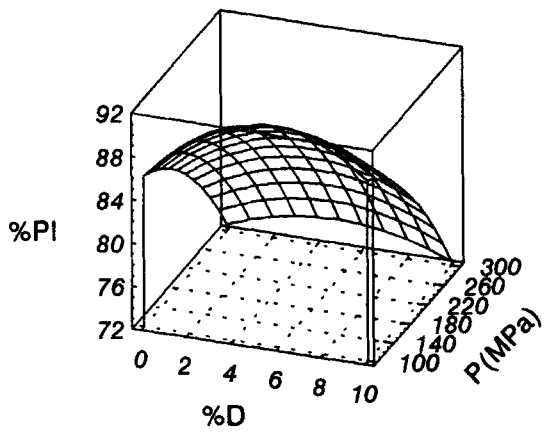

Figure 3. Surface response corresponding to the plasticity percentage parameter.

Table 5

Weight Uniformity and Variation Coefficient (VC), Breaking Strength (BS), Thickness, Friability (Fr), and Disintegration Time of Different Formulations

	Weight (mg)	BS (N)	Thickness (mm)	% Fr 100 rpm	Disintegration Time (sec)
Formulation A1	390	3.7	3.46	23.28	346.3
	VC = 2.18%	(0.5)	(0.01)		(88.6)
Formulation A2	391	53.2	2.92	2.19	>1800
	VC = 1.54%	(0.7)	(0.04)		
Formulation A3	416	97.2	2.92	0.98	>1800
	VC = 2.75%	(4.5)	(0.06)		
Formulation B1	380	0.0	3.52	30.62	10.8
	VC = 3.13%	(0.0)	(0.01)		(2.5)
Formulation B2	380	44.8	2.91	3.08	7.3
	VC = 3.31%	(9.0)	(0.01)		(2.7)
Formulation B3	400	64.8	2.89	1.36	11.5
	VC = 1.77%	(7.2)	(0.02)		(3.9)
Formulation C1	396	1.6	3.37	16.45	8.8
	VC = 2.09%	(0.4)	(0.01)		(1.8)
Formulation C2	402	48.3	2.99	2.22	8.2
	VC = 1.18%	(5.8)	(0.01)		(2.6)
Formulation C3	407	71.7	2.90	1.25	8.8
	VC = 1.27%	(3.8)	(0.01)		(3.9)

Tablets for all formulations passed the test for weight uniformity (European Pharmacopoeia, 3rd ed.). As expected, the values obtained in thickness tests (Table 5), indicative of uniformity of applied compression force, diminished with increasing pressure applied.

In relation to breaking strength (BS), the surface response (Fig. 4), based on the equation

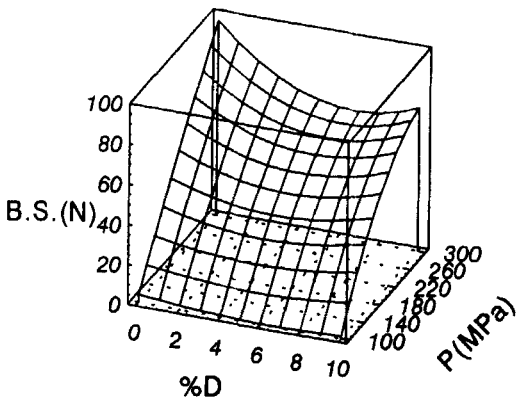

Figure 4. Surface response corresponding to breaking strength parameter.

$$BS\ (N) = -53.510 + 0.610P - 0.230D^2 - 3.67E - 4P^2 - 1.06E - 4DP^2 + 0.0031D^2P$$
$$r = 0.969$$

shows that, at low applied pressures, the breaking strength is independent of Explotab concentration. However, at higher applied pressures, the maximum densification obtained with 10% of Explotab produces a limited breaking strength lower than that at 0% concentration. Again, the influence of Explotab concentration has no appreciable effect on the friability surface, specially at high applied pressures. In contrast to the breaking strength, the friability decreases with the increase of applied pressure.

As shown in Table 5, the mean value of disintegration time (DT) decreases when the percentage of Explotab increases (formulation B and C versus formulation A). The following equation quantifies the effect of this variable under study.

$$DT = -1713.315 + 286.79D + 31.45P - 5.09DP - 2.96D^2 - 0.06P^2 + 0.007DP^2 + 0.14D^2P$$
$$r = 0.984$$

In this case, the surface response for this parameter (Fig. 5) shows, in agreement with Baie et al. (10), an

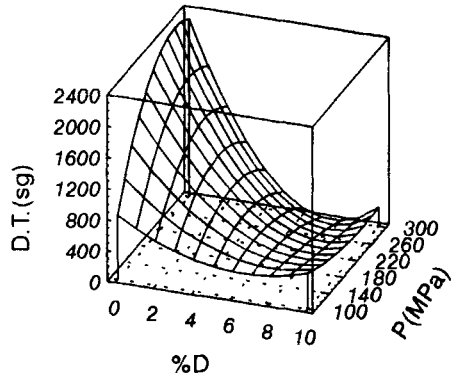

Figure 5. Surface response corresponding to the disintegration time parameter.

appreciable effect of percentage of disintegrant. However, although Baie et al. showed an increase of disintegration time when the compaction pressure increased, in our study the effect of applied pressure was important at low proportions of disintegrant (the disintegration time decreased when the applied pressure increased), but this effect diminished at concentration near 10%. Also, the response surface shows a certain level of Explotab, around 7%, at which the disintegration time was the shortest. At this level, the surface response is independent of the applied pressure.

We can conclude that the concentration of Explotab has a positive effect in relation to flow properties. The effect of applied pressure and disintegrant content was also found to be significant on all compressional parameters. We have found that experimental design can be a valuable tool used to establish the optimum manufacturing conditions, including content of disintegrant. In our study, the optimum content of Explotab was around 7%, clearly higher than that indicated by the manufacturer.

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