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Disintegrating efficiency of croscarmellose sodium in a direct compression formulation

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Abstract

The efficiency of croscarmellose sodium (Ac-Di-Sol®) 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 Ac-Di-Sol®, allowed the evaluation of microstructural, mechanical and disintegration properties of the tablets. Tablet properties evaluated were affected by both variables, while compression parameters were essentially dependent on applied pressure. The disintegration process was correlated with the densification behaviour, analysed by means of Heckel plots and force–displacement curves, and tablet microstructure, measured by using a mercury porosimeter. The shortest disintegration time was found for mixtures more prone to plastic deformation and densification at same level of applied pressure. These mixtures also revealed a finer pore structure. However, mixtures with higher yield pressures (i.e. less prone to plastic deformation) showed longer disintegration times and coarse pore structure. The different rearrangement of disintegrant particles in powder mixture is suggested to explain the dominant effect of the disintegrant bonding mechanism presented at a given mixture composition. According to our results, consolidation mechanism and microstructure analysis should be performed while optimizing disintegration response in tablets formulated with a disintegrant mainly acting by swelling mechanism. © 1997 Elsevier Science B.V.

Keywords: Disintegrant; Ac-Di-Sol®; Albumin tanate; Microstructure; Direct compression; Consolidation mechanism; Heckel

1. Introduction

A number of disintegrants, known as superdisintegrants, are available on the market. These disintegrants markedly improve tablet disintegra-

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tion, but their efficiency depends on the method of manufacture and/or physico-chemical characteristics of the tablet formulation.

These factors have been analysed in different papers using croscarmellose sodium and other superdisintegrants in tablets prepared by wet granulation. Gordon et al. (1990) used a computer-optimized experimental design to study the effect of incorporating croscarmellose sodium in wet granulated naproxen tablets. They conclude that tablets with the same total concentration of superdisintegrant dissolve faster when the superdisintegrant is included intragranularly. However, a subsequent investigation (Gordon et al., 1993a) shows that extragranular incorporation of croscarmellose sodium yields the best dissolution. These different results can be explained by the variables of the tablet system. Khattab et al. (1993), however, find that, in acetaminophen tablets, a shorter disintegration time is obtained when the disintegrant is distributed in the extragranular phase.

In the same way, Johnson et al. (1991) study the effect of tablet formulation solubility and hygroscopicity on the dissolution efficiency of three superdisintegants (sodium starch glycolate, crospovidone and croscarmellose sodium) in tablets prepared by wet granulation. The greater the overall hygroscopicity and solubility of the tablet formulation, the larger the decrease in the efficiency of the superdisintegrants. The aging at various storage conditions also decreases the dissolution efficiency of these three superdisintegrants (Gordon et al., 1993b). Croscarmellose sodium is affected by aging more than crospovidone or sodium starch glycolate.

In the last years, the role of this kind of disintegrant in tablets prepared by direct compression has been studied. Most of the reports carry out a comparison between sodium carboxymethylcelluloses and other commonly used disintegrating agents. So, Velasco et al. (1994) study the effect of the addition of three disintegrants on the tabletability of calcium-phosphate based materials for direct compression. The comparison of the disintegration times shows that the lowest values were found for Ac-Di-Sol® and Explotab®; on the opposite, Esma Espreng® was less effective as disintegrant. These two superdisintegrants also show better disintegrating properties than different starches (Visavarungroj and Remon, 1990).

Similarly, Bertoni et al. (1995) compare in some model tablets containing dicalcium phosphate dihydrate and a lubricant (talc), the disintegrating efficiencies of four sodium carboxymethylcelluloses. The effect of tablet solubility and higroscopicity on disintegrant efficiency of sodium starch glycolate, crospovidone and croscarmellose sodium has also been investigated by Gordon and Chowhan (1987). The results indicate that hygroscopic ingredients decrease the effectiveness of superdisintegrants. However, composite tablet solubility does not influence the effectiveness of those.

These authors carried out their studies with pure materials or disintegrant-other excipients mixtures, however, the results are not fully predictive of the disintegrant efficiency when the formulation contains drugs. For this reason, the aim of this present study is to assess the perfomance of the superdisintegrant Ac-Di-Sol®, in a direct compression formulation containing a poorly water soluble drug at high dosage.

In the present work, the drug used is albumin tanate, which precipitates the proteins of intestinal mucous membrane and creates a protective barrier. The therapeutic effect of this drug is, therefore, in the gut. Given that the albumin tanate is poorly water soluble, its bioavailabilty is more likely due to the disintegration process.

2. Materials and methods

2.1. Materials

Tablet composition includes the following ingredients: (1) albumin tanate (drug, Kirsch Pharm, Spain, batch 63059); (2) microcrystalline cellulose (filler, Mingtai® M102, Isisa, Spain, batch 70821); (3) croscarmellose sodium (superdisintegrant, Ac-Di-Sol®, Isisa, Spain, batch 5010); (4) colloidal silica (glidant, Syloid®, Grace, Germany, batch AI-1) and (5) stearic acid (lubricant, Estearina® L2SH José Escuder, Spain, batch 106). Powders were stored under controlled tem-

perature (20°C) and humidity (RH = 40%) conditions.

2.2. Formulations

The formulations were prepared as follows. Firstly, drug (71% w/w), Mingtai® M102 and Ac-Di-Sol® (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.

2.3. Material density

Material density of the powders was determined, in triplicate, by an air comparison pycnometer (quantachrome stereopycnometer, Miami, FL) using helium as an inert gas.

2.4. Tableting

The compression characteristics of the powders were investigated by using an instrumented single-punch tablet machine (Bonals, model AMT 300, Barcelona, Spain) with strain gauge HBM YL6 connected to dynamic amplifiers (NEC Sanei, Tokio, Japan) and inductive displacement transducers (HBM Darmstadt, Germany) (Muñoz-Ruiz et al., 1995). Powder (400 mg) were manually filled into the die (12 mm). Flat compacts were prepared at fixed applied pressure (100, 200 or 300 MPa) to study compression properties of the mixtures. In every case, six parallel tablets were compressed. During compression, upper and lower punch forces and displacements were monitored. Also, to study tablet properties, the mixtures were tableted in a single-punch machine (Bonals, model AMT 300, Barcelona, Spain) running at 30 cycles/min and equipped with a forced feeding system.

2.5. Compression equations

The relations between the applied pressure and the density of the powder columns were analysed by means of the Heckel (Heckel, 1961a,b) equation:

$$\ln \frac{1}{1-D} = KP + A$$

which relates the packing fraction or relative density D (i.e. ratio between apparent density of a powder bed and the material density) to the applied pressure, P. The slope of the straight line portion, K, was generally expressed as a reciprocal, and was referred to as mean yield pressure. The least-squares method was used for obtaining the accurate slope and intercept values. The linear portion of the Heckel function was determined on the basis of the best fit to the linear model from consecutive data. The criterion to estimate the fit was obtained from the F-ratio between the model and the residual. The linear portion coincided with the group of successive data with the highest F-ratio.

2.6. Physical testing

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

2.6.1. Weight

The weight of 20 tablets was determined individually using an analytical Mettler AE 50 balance (Greifensee, Switzerland) and the mean weight and coefficient of variation (CV) were calculated.

2.6.2. Breaking force

This was determined for 6 tablets using a Schleuninger-2E apparatus (Greifensee, Switzerland).

2.6.3. Friability

Weight loss through friability was determined for 10 tablets after 4 min in an Erweka TA (Heusenstamm, Germany) apparatus at 25 rpm.

2.6.4. Distintegration time

Disintegration testing (6 tablets) was performed at 37°C in HCl 0.1 N medium using the European Pharmacopoeia apparatus (Erweka ZT3, Erweka, Heusenstamm, Germany) without discs.

Table 1
Average of force (EF_{max}), apparent net work (W_{AN}) and plasticity (%PI) from different formulations

Formulation	EF_{max} (N)	W_{AN}(J)	%PI
A1	211.7 (0.0)	8.3 (0.3)	85.4 (1.1)
A2	282.3 (12.8)	13.1 (0.1)	82.5 (2.0)
A3	341.8 (25.7)	15.2 (0.2)	72.1 (0.4)
B1	104.0 (6.4)	9.3 (0.0)	86.9 (1.3)
B2	282.3 (12.8)	15.3 (1.2)	88.5 (5.4)
B3	416.1 (126.7)	16.9 (1.1)	72.1 (2.5)
C1	243.3 (14.0)	8.3 (0.2)	87.2 (0.7)
C2	364.1 (12.8)	14.5 (0.3)	82.1(0.9)
C3	252.6 (12.8)	17.9 (1.5)	71.8 (2.5)

A, B and C correspond to 0, 5 and 10% of Ac-di-sol®.
1, 2 and 3 correspond to 100, 200, and 300 MPa.

2.6.5. Mercury intrusion porosimetry

A Quantachrome Autoscan 33 with 3 ml penetrometer for solids was employed. Working pressures covered the range 0.6–33 000 psi (corresponding to 2.10^{-6}–32 Å pore size). The total porosity and the pore size distribution were determined in triplicate for each formulation.

2.7. 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 Ac-Di-Sol® (D) at three levels (Formulations A, B and C corresponding to 0, 5 and 10% of Ac-Di-Sol®; 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 were obtained as regression equations by stepwise multiple regression.

3. Results and discussion

The mean compression parameters for the different formulations are shown in Table 1. The corresponding ANOVAs (Table 2) show that many terms are significant.

The maximum ejection force (EF_{max}) is defined as the maximum force of the lower punch during the ejection of the tablet from the die (Waring et al., 1987). The results show that all formulations carry out the requirements proposed by Bolhuis and Lerk (1973), with values lower than 750 N. The following equation, fitted using stepwise multiple linear regression, quantifies the effect of variables under study.

$$EF_{max}(N) = 127.16 + 0.75P$$

$$[r = 0.4079;\ p < 0.01]$$

Although the correlation coefficient is low due to deviation of data of formulation C3, this equation shows, in agreement with Sadjady and Rubinstein (1993), that the ejection force is influenced directly by the pressure. However, the

Table 2
Values of F-ratio obtained for the different parameters in the analysis of variance

Parameter	Ac-Di-Sol® Percentage (D)	Applied Pressure (P)	Interaction ($D \times P$)
EF_{max}	0.43**	29.53*	10.71*
W_{AN}	6.25*	259.05*	1.94**
%Pl	2.82**	95.94*	2.16**
BF	6.49*	510.31*	30.46*
%Fr	544866.78*	999999.99*	459418.11*
DT	11440.03*	1600.80*	1572.01*
Por	8.03*	100.12*	1.82**

Abbreviations: EF_{max}, maximum ejection force; W_{AN}, apparent net work; %Pl, plasticity; BF, breaking force; %Fr, percentage of friability; DT, disintegration time; Por, total porosity.
*$p < 0.05$.
**$p > 0.05$.

percentage of disintegrant does not have considerable effect. No differences of note were found between the ejection force and the normalized parameter (Stamm and Mathis, 1975).

Apparent net work (W_{AN}) is the work required to compress the tablet. This parameter is calculated by subtracting work done due to friction and expansion from the applied work. As we can see in Table 1, this parameter increases as the applied pressure in the formulations is increased. Also, the mean value of W_{AN} for the formulations with disintegrant (B and C) was higher than for the formulation without disintegrant (A). This is probably due to the lower percentage of filler in those formulations. The following equation was obtained:

$$W_{AN}(J) = 0.09 + 0.09P + 5.4 \times 10^{-4}DP - 1.4710^{-4}P^2$$

$$[r = 0.9419;\ p < 0.01]$$

This equation for apparent net work demonstrates that the applied pressure has an important effect, while percentage of disintegrant only affects by means of its interaction with applied pressure, giving a term with a low coefficient.

The plasticity (%Pl) values calculated from the following relation (Stamm and Mathis, 1975):

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

where W_{EXP} = expansion work and W_{AN} = apparent net work were between 71 and 88%, lower than those obtained for tablets compressed from the plain microcrystalline cellulose used as filler in this study (94.3%) (Muñoz-Ruiz et al., 1994).

The equation fitted using multiple stepwise regression was:

$$\%Pl = 78.47 + 0.13P - 5.11 \times 10^{-4}P^2$$

$$[r = 0.8438;\ p < 0.01]$$

The response surface, based on this equation (Fig. 1) shows a quadratic relation between plasticity and applied pressure. Although a small increase in %Pl is observed at low levels of pressure, this parameter decreases when applied pressure is increased. The rise in the expansion of tablet at high pressures could explain these results.

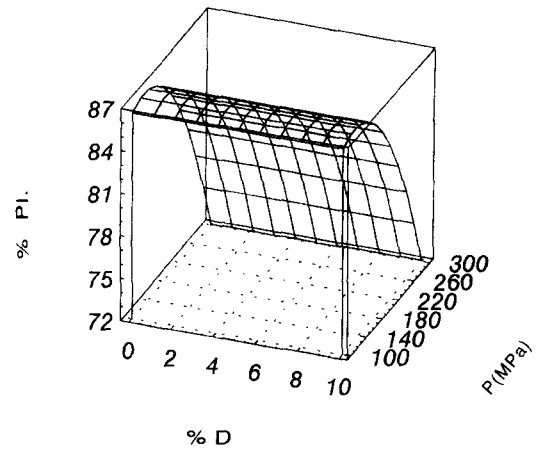

Fig. 1. Response surface corresponding to plasticity.

The percentage of disintegrant does not have an appreciable effect upon plasticity. However, Velasco et al. (1994) showed an increase of this parameter with the addition of disintegrant, especially by adding Explotab® in dicalcium phosphate tablets. In this case, an additional effect of the disintegrant overcoming friction between particles of filler and die wall could assist expansion during decompression.

The influence of the disintegrant on weight uniformity, breaking strength, thickness, friability, disintegration time and porosity is shown in Table 3.

Tablets for all formulations passed the test of weight uniformity (Farmacopea Europea, 1988).

In relation with breaking force (BF), the response surface (Fig. 2a), based on the equation:

$$BF(N) = -89.5 + 1.21P - 2.1 \times 10^{-3}P^2$$

$$[r = 0.8443;\ p < 0.01]$$

is independent of disintegrant percentage. Therefore, the concentration of Ac-Di-Sol® does not have, in agreement with Chukwu (1993), an important effect upon the binding properties of materials. However, Khan and Rhodes (1973) show a decrease in breaking force when the concentration of superdisintegrant increases for formulations containing two insoluble direct compression systems.

Table 3
Tables test results

Formulation	Weight (mg)	BF (N)	T (mm)	Fr (%)	DT (s)	Por	P.M.D. (Å)
A1	390 (8.5) C.V. = 2.18%	3.7 (0.5)	3.45 (0.01)	23.3	346 (89)	0.21 (0.00)	635
A2	391(6.0) C.V. = 1.54%	53.2 (7.7)	2.92 (0.04)	2.2	>1800	0.13 (0.01)	411
A3	416 (15.4) C.V. = 2.75%	97.2 (4.5)	2.92 (0.06)	0.9	>1800	0.09 (0.00)	299
B1	404 (14.9) C.V. = 3.71%	22.7 (1.9)	3.36 (0.02)	5.7	15 (4)	0.18 (0.00)	549
B2	400 (8.1) C.V. = 2.03%	62.0 (9.4)	2.91 (0.02)	1.5	11 (4)	0.12 (0.00)	381
B3	402 (13.1) C.V. = 3.28%	77.3 (2.6)	2.82 (0.03)	0.4	6 (1)	0.11 (0.00)	345
C1	376 (9.0) C.V. = 2.40	5.0 (0.8)	3.35 (0.02)	28.8	3 (2)	0.21 (0.00)	691
C2	434 (7.4) C.V. = 1.72%	91.7 (12.1)	3.11 (0.03)	1.1	14 (10)	0.14 (0.03)	453
C3	398 (7.4) C.V. = 1.87%	83.5 (8.1)	2.82, (0.03)	2.1	24 (3)	0.13 (0.01)	409

Abbreviations: BF, breaking force; T, thickness; Fr, friability; DT, disintegration time; Por., total porosity; P.M.D., pore mean diameter.

On the other hand, the applied pressure has a large influence. The breaking force increases when the applied pressure rises, obtaining the maximum value at 288 MPa (calculated by means of partial derivatives).

The tendency observed for plasticity demonstrated that a higher anount of stored elastic energy is only obtained when applied pressure exceeded this limit (288 Mpa). Then, the release of this energy overcomes bond strength during decompression.

As expected, the values obtained in the thickness test (Table 3), which indicate a uniformity of applied pressure, diminish when the pressure increases.

As we can see in the response surface for friability (%Fr) (Fig. 2b), this parameter decreases when applied pressure is increased up to approximately 250 MPa. These results correlate well with breaking force. Probably, the level of the stresses in the tablet is approximately uniform. In this way, the surface of tablets, especially top and bottom edges, which the friability testing attempts to quantify, behaves in the same way that the whole tablet in breaking strength testing.

Furthermore, the percentage of disintegrant does not have an appreciable effect on friability, as it is shown in the corresponding equation:

$$\%\mathrm{Fr} = 54.11 - 0.43P + 8.6110^{-4}P^2$$

$$[r = 0.6434;\ p < 0.01]$$

As we can see in Table 3, the mean values of disintegration time (DT) decrease when Ac-Di-Sol® is added (formulation B and C vs. formulation A). In this case, the following equation was obtained:

$$\mathrm{DT(s)} = -849.61 + 16.55P - 1.99\mathrm{DP} - 0.02P^2 + 0.13PD^2 \quad [r = 0.9444;\ p < 0.01]$$

The response surface for this parameter (Fig. 3a) shows an important effect of percentage of

disintegrant. Disintegration time decreases when Ac-Di-Sol® concentration increases, just to a minimum value corresponding to a 7.6% of superdisintegrant (calculated by means of partial derivatives). However, we observe a slight increase of disintegration time at a concentration level near to 10%.

The effect of applied pressure is important at low proportions of disintegrant (the disintegration time increases when the applied pressure rises), but this effect diminishes at concentration near to 10%.

Mercury intrusion porosimetry was carried out to determine the effect of the microporous tablet structure on the disintegration of albumin tanate tablets, and also to correlate this parameter with disintegration test.

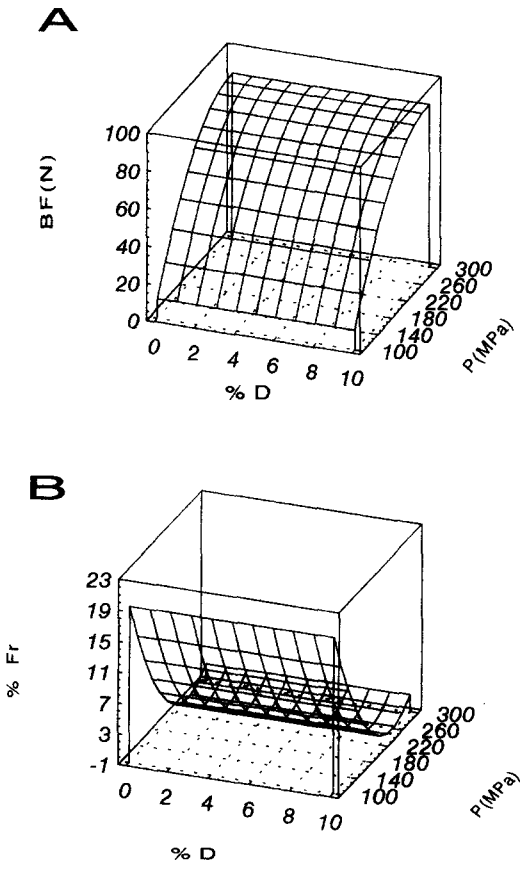

Fig. 2. (A)Response surface corresponding to breaking force and (B) response surface corresponding to friability.

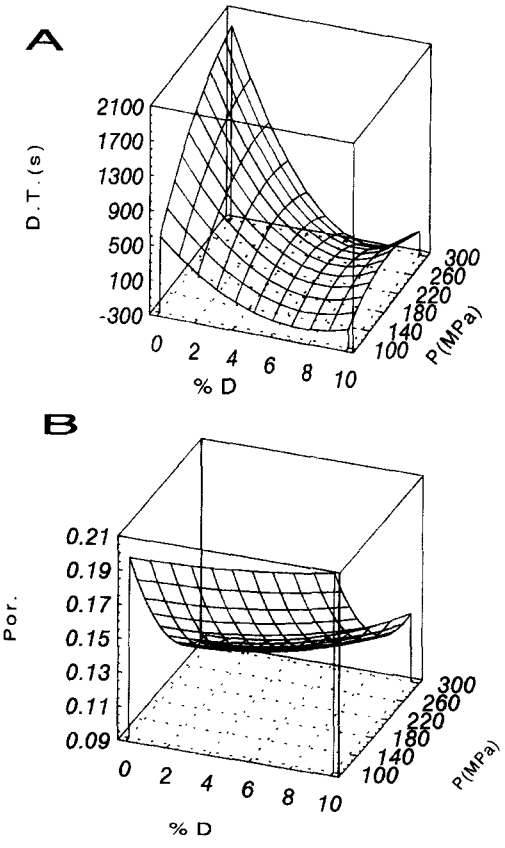

Fig. 3. (A) Reponse surface corresponding to disintegration time (B) response surface corresponding to total porosity.

The equation fitted for the total porosity (Por) was:

$$\text{Por} = 0.31 - 1.4 \times 10^{-3}P + 2.34 \times 10^{-6}P^2 + 1.09 \times 10^{-6}PD^2 \quad [r = 0.9038;\ p < 0.01]$$

In a same formulation, the total porosity and pore mean diameter decrease when applied pressure increases (Table 3), as expected, according to different studies (Selkirk and Ganderton, 1970). However, an increase of total porosity is observed (Fig. 3b) at high pressures (upper 288 MPa), especially when the concentration of disintegrant is close to 10%. The increase of the expansion could explain the event mentioned above.

The characteristic tendency to plastic deformation can be seen in Fig. 4, with typical Heckel plots of A, B, C formulations compressed at 100

MPa. During the compression stage of these materials, the pressure range used in tableting formulation B up to a value greater than the true density of the material, demonstrating a 'negative porosity'. This behaviour during tableting was previously reported (Doelker, 1988) for several pharmaceutical materials.

This correlates well with the values of yield pressure found for the formulations (A, 71.67; B, 47.16; C, 87.37). Formulation B was more prone to plastic deformation than the others.

Force–displacement curves in Fig. 5 also support the characteristic behaviour of formulation B. For this formulation, above 32 kN, data of compression and decompression were superimposed. Thus, the same sequence was observed for mean yield pressure, pressure producing zero porosity and pressure corresponding to theoretical point at which no further densification due to intermolecular and intramolecular bonds can occur (Doelker, 1988).

On the basis of all these data, it is possible to establish a correlation between particles deformation, tablet porosity and disintegration process according to the two disintegration mechanisms involved with Ac-Di-Sol®: porosity and strong swelling, being the last one the most important (Bolhuis et al., 1981, 1982).

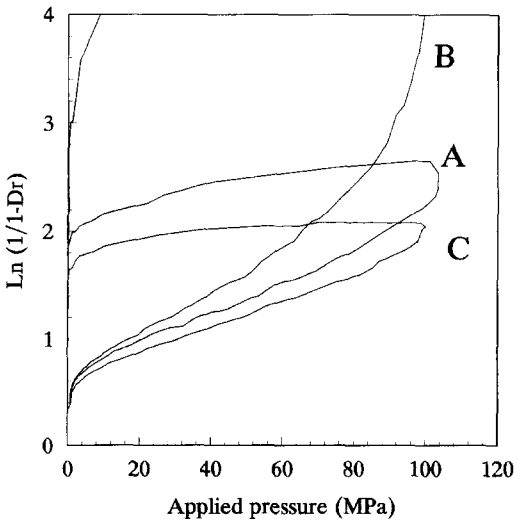

Fig. 4. Typical Heckel plots of formulations A, B, C.

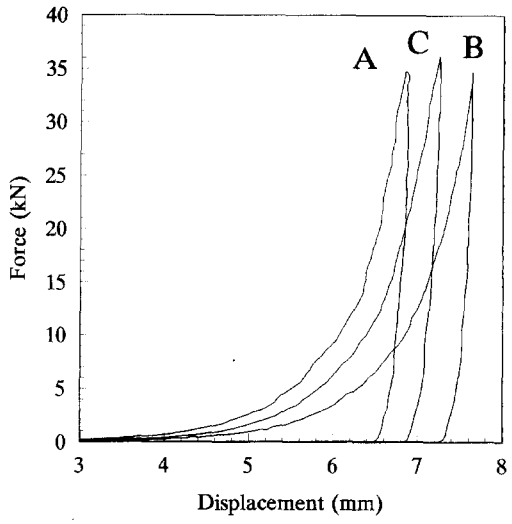

Fig. 5. Force-displacement curves of formulations A, B, C, compressed at 300 WPa.

When the concentration of superdisintegrant is low, the total porosity and pore mean diameter decrease when applied pressure increases and, consequently, the disintegration time increases, as has been also reported by a number of authors (Selmeczi and Kedvessy, 1970; Borzunov and Shevchenko, 1967; Fox et al., 1974).

When the percent of superdisintegrant increases, but does not reach the level (7.6%) at which disintegration time is minimum, the swelling process is the predominant mechanism. Pore size distribution (Fig. 6) demonstrates a finer pore structure at these levels of disintegrant percentage. Under these conditions, the superdisintegrant makes enough pressure in the pores of the tablet as to produce an efficient disintegration (Berry and Ridout, 1950; Ganderton and Fraser, 1970). Although the rates of capillary penetration in tablets of narrower pore size distribution are lower than those for structures of wide pore size distribution, larger parts of pore structure participate in liquid uptake. So, the final saturation volume is superior at the intermediate levels of disintegrant (Selkirk and Ganderton, 1970).

This correlates well with the deformation tendency of the formulations on the basis of Heckel parameters and compression profile. The particles

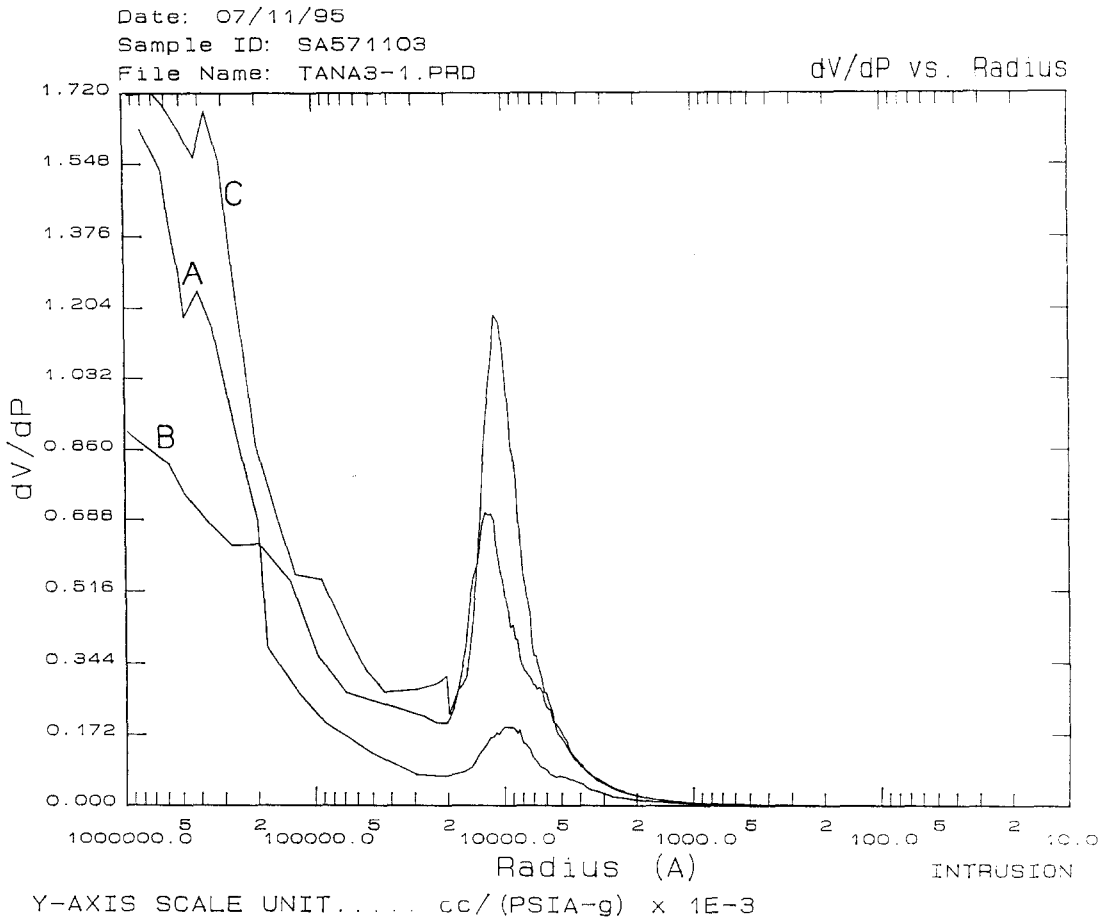

Fig. 6. dV/dP versus pore radius of formulations A, B, C compressed at 300 MPa. Percentage of disintegrant: (A) 0% (B) 5% (C) 10%. The volume of mercury is normalized by sample weight.

of disintegrant in powder mixtures probably make up a continuous network or skeleton which tends to facilitate the plastic deformation (i.e., lower yield pressure and higher densification at same compaction pressure) and disintegration process. This behaviour has been reported by several authors (Sheikh-Salem and Fell, 1981; Vromans and Lerk, 1988; Ilkka and Paronen, 1993) for mixtures of pharmaceutical materials. It is then suggested that there is a limit of concentration of disintegrant (in this study, probably close to 7.6%) to create this skeleton.

At higher concentrations of superdisintegrant (above 8%), the decrease of disintegration time not only is less remarkable but also can increase. This may be explained by the relatively coarse pore structure noticed in Fig. 6 at these percentages of disintegrant. Rapid penetration of the largest capillaries isolates other areas of finer pore structure which air cannot escape. These areas then make no contribution to the overall uptake of liquid (Selkirk and Ganderton, 1970).

According to yield pressure values, the higher disintegration concentration, the less prone to plastic deformation. During the compression process, particle deformation strongly enhanced porosity reduction (Nystrom et al., 1993), especially porosity due to the largest pores (Stanley-Wood and Johansson, 1980). Besides the different rearrangement of particles at these mixtures com-

positions, differences in water content, as well as differences in surface properties, also might have effect on densification behaviour at high level of disintegrant.

The whole analysis of all these factors has demonstrated that the relationship between mixture composition and compression and disintegration behaviour was non linear. Thus, according to our results, the best tablet strength is obtained by applying pressures in the range 250–288 MPa and the optimum concentration of the disintegrant in the tablet formulation is likely to be in the range of 5–8% w/w.

Acknowledgements

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