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Analysis of the physical characterization and the tabletability of calcium phosphate-based materials

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Abstract

The rheological properties of the new excipients A-, Di- and Tri-tab® were in general better than those of Emcompress®, whereas a mixture of Emcompress® with magnesium stearate exhibited the best flow characteristics and the lowest coefficient of tablet weight variation. Granulometry of the excipients demonstrates that Tri-tab® has a maximum mean diameter and a wide particle size distribution, while Emcompress® has a particle size distribution similar to that of Di-tab®. Different compression properties, namely, net work, compactibility, plasticity and ejection work, were evaluated after adding a hydrophobic lubricant to the wall of the die. The compressional properties demonstrated the values of the friction parameters to be insufficient in the case of Di- and Tri-tab® powders, therefore, lubrication would be a major factor in tableting with these excipients for direct compression. Absolutely different compressional behavior of Di-tab was observed. Moreover, the parameters obtained from the Heckel in die tablet method were calculated in order to establish the comparative consolidation mechanisms in the excipients under study. Emcompress® showed a lower extent of brittle fracture and greater plasticity than the other calcium phosphate-based excipients.

Key words: Direct compression excipient; Rheology; Calcium phosphate-based material; Consolidation mechanism; Particle size distribution; Tableting properties

1. Introduction

The successful application of direct compression excipients in pharmaceutical tableting depends on the development of suitable excipients that are free flowing, highly compressible, physiologically inert and chemically compatible with the active ingredients (Garr and Rubinstein, 1991). Therefore, new excipients might be designed deliberately, on the basis of what are now known to be desirable properties from the viewpoint of pharmaceutical technology.

At present, the evaluation of excipients in relation to flow and compression characteristics is an important technological process. This is especially true for direct compression excipients, since in this case it is only the characteristics of the excip-

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ients that exert an influence on both properties. Concerning this aspect, a number of papers have been published regarding the tableting properties of direct compression excipients (Bolhuis and Lerk, 1973; Ho et al., 1977). However, various authors have recently accomplished comparative evaluations of excipients pertaining to the same chemical groups, such as lactose-based materials (Whiteman and Yarwood, 1988; Muñoz-Ruiz et al., 1993) and microcrystalline cellulose excipients (Doelker et al., 1987). In this sense, the goal of the present investigation was to evaluate the rheological properties and compression characteristics of calcium phosphate-based materials used as direct compression excipients.

2. Materials and methods

Four excipients for direct compression were used in this study: Emcompress® (dibasic dicalcium phosphate dihydrate; batch 1859, Julia/Parrera, Barcelona, Spain); A-tab® (dibasic dicalcium phosphate, anhydrous, granular; batch 5007, Rhône-Poulenc Basic Chemicals, Chicago, U.S.A.); Di-tab® (dibasic dicalcium phosphate dihydrate, unmilled; batch 6726, Rhône-Poulenc Basic Chemicals, Chicago, U.S.A.); Tri-tab® (tricalcium phosphate, anhydrous; batch 2043, Rhône-Poulenc Basic Chemicals, Chicago, U.S.A.); and magnesium stearate as lubricant (batch 2092, Acofarma, Barcelona, Spain). Powders were stored under controlled temperature (20°C) and humidity (RH = 40%) conditions. The sampling size for each excipient was 1 kg.

The techniques used for determining the static repose angle (σ_{st}) and compressibility on tamping are described in detail in earlier studies (Borrero et al., 1988; Muñoz-Ruiz et al., 1988). The dynamic angle of repose (σ_{dy}) was measured according to the rotating cylinder method (Hedge et al., 1985) (stainless-steel cylinder with an internal diameter of 80 mm). Particle size distributions were determined using sieves of 500, 450, 400, 350, 300, 250, 200, 175, 150, 125, 100, 75, 50 and 25 μm (C.I.S.A. Barcelona, Spain) in a vibrator sieve (Retsch, Haan, Germany). The true density of each powder was determined using a pycnometer (Model SPY-3 stereopycnometer, Quantachrome, Syosset, NY, U.S.A.). The gas used was helium.

The compression characteristics of the powders were investigated on an instrumented single punch machine (Bonals AMT 300, Barcelona, Spain) with HBM YL6 strain gauges connected to dynamic amplifiers (NEC San-ei, Tokyo, Japan) and inductive displacement transducers (HBM, Darmstadt, Germany). A quantity of powder to produce tablets of thickness 2.5 mm at zero theoretical porosity was manually filled into the die (12 mm). Flat compacts were prepared at fixed crushing force (40 N) to study the variations in the compression properties of the powders. The die was lubricated with a chloroformic solution of stearic acid (5% w/v).

To examine the tablet properties, the excipients were mixed with 0.5% by weight of magnesium stearate for 5 min in a 0.5 l plastic vessel in a asymmetric biconic-shape mixer (Retsch, Haan, Germany) at 48 rpm. The mixture was tableted in a single punch tablet machine (Bonals, Model AMT 300, Spain) running at 30 cycles/min and equipped with a forced feeding system. The resulting tablets were convex faced (diameter = 9 mm) and prepared at fixed crushing force (40 N). The weight (mg) of each of 20 individual tablets was determined using an electronic balance (Mettler AE 50, Mettler Instrumentate, Grifensee, Switzerland).

The crushing strength was determined immediately after compression in a commercially available hardness tester (Schleuniger-2E, Dr K. Schleuniger, Greifensee, Switzerland).

Friability was evaluated from the weight loss of 10 tablets which were tumbled for a total of 100 revolutions using an Erweka TA (Erweka TA. Erweka, Heusenstamm, Germany) friability tester.

The thickness of 10 tablets was measured using a Mitutoyo MDC-M293 micrometer (Mitutoyo, Tokyo, Japan).

Disintegration testing (six tablets) was performed at 37°C in 0.1 N HCl medium using the European Pharmacopoeia apparatus (Erweka ZT3, Erweka, Heusenstamm, Germany) with discs.

3. Results and discussion

In Table 1, the static (σ_{st}) and dynamic (σ_{dy}) angles of repose of the excipients and of the mixtures with magnesium stearate have been listed. Emcompress® showed the maximum angles of repose and Tri-tab® the minimum, the excipients A-tab® and Di-tab® demonstrating intermediate values. The greatest decrease in static and dynamic angles of repose was evident for Emcompress® when mixed with magnesium stearate. In contrast, the mixture of Tri-tab® scarcely showed an increase.

Our results are consistent with those of Delattre et al. (1973) who reported that materials with an angle of repose less than 40° were classifiable as free-flowing powders. However, we did observe free flow in Emcompress® with a static angle of repose (Table 1) greater than 40° (45°).

Table 2 shows the characteristic values of the packing distribution. Emcompress® was found to be the excipient showing the highest Hausner index, indicative of interparticle friction (Hausner, 1972), whilst Tri-tab® presented the lowest value. The compressibility factor (Carr, 1965) exhibited the same trend in magnitude as the Hausner index and dynamic angle of repose. The value of the Hausner index for Emcompress® was consistent with that (1.2) determined by Delattre et al. (1973). Furthermore, this value was the highest and the closest of the values for the excipients under study to the Stamm value (Stamm and Mathis, 1977), i.e., 1.28. The addition of magnesium stearate minimized the Hausner index and compressibility factor in the case of Emcompress®, whereas it led to an increase in this parameter for Tri-tab®. This finding may be explained on taking into account the particle size of Tri-tab® which is clearly greater than that of Emcompress® and therefore the flow characteristics (Jones and Pilpel, 1966) of the former will be improved to a lesser extent by the addition of magnesium stearate as compared with Emcompress®.

Typical parameters of normal distributions are presented in Table 3: Mean weight diameter (d_w), standard deviation, and coefficient of variation, kurtosis and skewness. Tri-tab® has a maximum mean diameter (306.2) and, accordingly, free or gravitational flow (Jones and Pilpel, 1966). Emcompress® has a minimum mean diameter (159.2) similar to the d_w of Di-tab® (163.1). Furthermore, Di-tab® shows a standard deviation (46.0) comparable with that of Emcompress® (40.1). In the case of Di-tab® and Emcompress® (both dibasic dicalcium phosphate dihydrates), differences in the packing properties of products can probably be ascribed to differences in the particle size distribution and particle shape (Muñoz-Ruiz et al., 1992). Hence, Di-tab® displays the highest coefficient of kurtosis and skewness and therefore a narrow particle size distribution with the greatest asymmetry of the particle size distribution (Gutierrez Cabria, 1988). All the excipients under study possessed less than 1% of fines (particles < 50 μm).

To evaluate the compressional properties of the excipients with lubrication of the die, the averages of the parameters, ratio between crushing force and mean applied force to make the tablet, net work, compactibility (ratio between tensile strength and net work) (York and Pilpel, 1975), ejection force (EF), work of ejection, resid-

Table 1
Values of repose angles (average of three experiments ± S.D.) (in °)

Material	Static angle of repose σ_{st}		Dynamic angle of repose σ_{dy}	
	Without lubricant	With lubricant	Without lubricant	With lubricant
Emcompress®	45.0 ± 2.0	36.0 ± 0.4	38.0 ± 0.4	28.2 ± 0.8
A-tab®	38.6 ± 0.0	37.5 ± 1.1	30.0 ± 1.0	29.0 ± 1.0
Di-tab®	36.2 ± 0.8	35.3 ± 1.5	34.0 ± 1.0	30.1 ± 0.7
Tri-tab®	35.8 ± 0.3	38.9 ± 1.2	27.3 ± 1.2	27.8 ± 0.9

Table 2
True density (ρ), tap density (ρ_t), bulk density (ρ_b), Hausner index (H) and compressibility factor (C) (average of five experiments ± S.D.)

Material	ρ (g/cm^3)	ρ_t (g/cm^3)	ρ_b (g/cm^3)	H	C
Emcompress®	2.2244 ± 0.0030	1.086 ± 0.005	0.891 ± 0.012	1.219 ± 0.010	10.24 ± 0.23
Emcompress® + lubricant	2.1528 ± 0.0831	1.090 ± 0.010	0.921 ± 0.017	1.180 ± 0.022	5.50 ± 0.15
A-tab®	2.6611 ± 0.0030	0.581 ± 0.033	0.489 ± 0.0180	1.187 ± 0.030	6.21 ± 2.50
A-tab® + lubricant	2.6228 ± 0.0100	0.931 ± 0.045	0.798 ± 0.021	1.187 ± 0.028	8.60 ± 0.19
Di-tab®	2.2471 ± 0.0025	1.086 ± 0.000	0.912 ± 0.022	1.191 ± 0.020	9.62 ± 1.34
Di-tab® + lubricant	2.2458 ± 0.0071	1.092 ± 0.028	0.920 ± 0.017	1.187 ± 0.021	7.34 ± 0.42
Tri-tab®	2.7178 ± 0.0226	0.917 ± 0.008	0.803 ± 0.016	1.141 ± 0.010	3.02 ± 0.53
Tri-tab® + lubricant	2.7086 ± 0.0024	0.921 ± 0.005	0.841 ± 0.015	1.192 ± 0.013	3.02 ± 0.41

ual lower punch force (RLPF), lubrication coefficient (R) and plasticity (Stamm and Mathis, 1976) in percent (% Pl), were calculated with values obtained for tablets of 40 N crushing strength. The parameters are listed in Table 4.

Table 4 shows that the ratio between crushing force and mean applied force and compactibility of Di-tab® were lower than in the other excipients. A-tab® exhibited the highest ratio while Tri-tab® and A-tab® presented similar compactibility values, the latter being the highest. Emcompress® demonstrated lower values compared with these two excipients.

Fig. 1 depicts the compression curves of the calcium phosphate-based materials. In Fig. 1, a considerable difference in compressional behavior is evident for Di-tab® as compared with the other materials under study, with an area under the curve of 10.45 J. In addition, it may be observed that the area under the curve of Emcompress® (7.16 J) scarcely differs with regard to that of A-tab® (6.71 J) and Tri-tab® (6.39 J).

The plasticity of calcium phosphates showed statistically significant differences among all the excipients (Fisher test, $F_{3,8} = 138.32 > 4.07$, $p = 0.95$). Di-tab® exhibits the lowest plasticity, Emcompress® showing the highest value.

Lubrication of the die using a chloroformic solution of stearic acid 5% w/v was necessary in order to make tablets. Under these experimental conditions, in general, the friction was observed to be considerable in all the cases. The results demonstrated that only A-tab® fulfilled the requirements for direct compression excipients as proposed by Bolhuis and Lerk(1973) who established that the values of R must be greater than 0.9 and the ejection forces lower than 750 N.

Fig. 2 shows profiles of the ejection force vs time. It can be seen from Fig. 2 that high ejection

Table 3
Evaluation of normal size distribution

Material	d_w (μm) (± S.D.)	Coefficient of variation	Coefficient of kurtosis	Coefficient of skewness
Emcompress®	159.2 ± 40.1	0.2517	0.0209	0.7280
A-tab®	175.3 ± 50.6	0.2887	5.4789	1.6405
Di-tab®	163.1 ± 46.0	0.2816	7.9291	1.6686
Tri-tab®	306.2 ± 76.4	0.2495	0.4484	−0.9919

Table 4
Compressional properties of the excipients (average of five experiments ± S.D.)

Excipient	Crushing/mean applied forces ($\times 10^{-3}$)	Net work (J)	Compactibility (MPa/J)	Ejection force (N)	Work of ejection (J)	Residual lower punch force (N)	Lubrication coefficient	Plasticity (%)
Emcompress®	3.541 ± 0.710	6.036 ± 0.253	0.1149 ± 0.0328	927.9 ± 425	2.678 ± 0.267	775.6 ± 439	0.872 ± 0.072	90.06 ± 1.67
A-tab®	4.139 ± 0.147	5.600 ± 0.173	0.1239 ± 0.0270	253.5 ± 18.6	0.013 ± 0.003	133.0 ± 16.6	0.992 ± 0.012	87.07 ± 0.82
Di-tab®	1.667 ± 0.323	6.835 ± 0.312	0.1015 ± 0.0235	1523 ± 1102	3.860 ± 0.575	1295 ± 844	0.838 ± 0.060	77.57 ± 1.74
Tri-tab®	3.325 ± 0.794	5.533 ± 0.700	0.1234 ± 0.0355	2095 ± 512	5.911 ± 0.673	1071 ± 135	0.723 ± 0.041	87.72 ± 0.57

forces are required in the cases of Di-tab® and Tri-tab® and that the form of the curve exhibits two or three peaks, while Emcompress® demonstrates lower ejection forces and the contour of the curve corresponds to the ejection force decreasing uniformly with time and without various peaks. The profile of A-tab® for ejection force was closer to the baseline. The patterns of variation in ejection force and work of ejection were consistent with the observed values for the lubrication coefficient (Table 4). The magnitude of this effect conformed to the following descending rank order: Tri-tab®, Di-tab®, Emcompress® and A-tab®.

The results derived using the Heckel tablet-in-die method (Humbert-Drotz et al., 1978) from the experimental data obtained (N) are gathered in Table 5: the parameters involved are the intercept density of the linear regression (Da), density contribution to movement and rearrangement (Db′), relative density of precompression (D'_0), yield pressure (Py), correlation coefficient (r) and the values of F-tests for significance of regression (F).

Several authors have used the Heckel equation to describe the compaction behaviour of Emcompress® (Rue and Rees, 1978; Paronen, 1986) as a brittle material which undergoes compression, revealing an extensive fracture. The results are in agreement with the values reported by Humbert-Droz et al. (1982) and Paronen (1986), i.e., yield pressures greater than 250 MPa and Db′ values (Table 5) above 0.160. A considerable difference in compression behaviour between Di-tab® and the other materials is evident from the data. Hence, this excipient exhibited the highest values of the yield pressure (342.6 MPa) and Db′ (0.251), and thus the strongest fragmentation propensity. The yield pressures for Emcompress®, A-tab® and Tri-tab® scarcely differed. A-tab® displayed the lowest value of Db′ (0.161), revealing significant differences with the

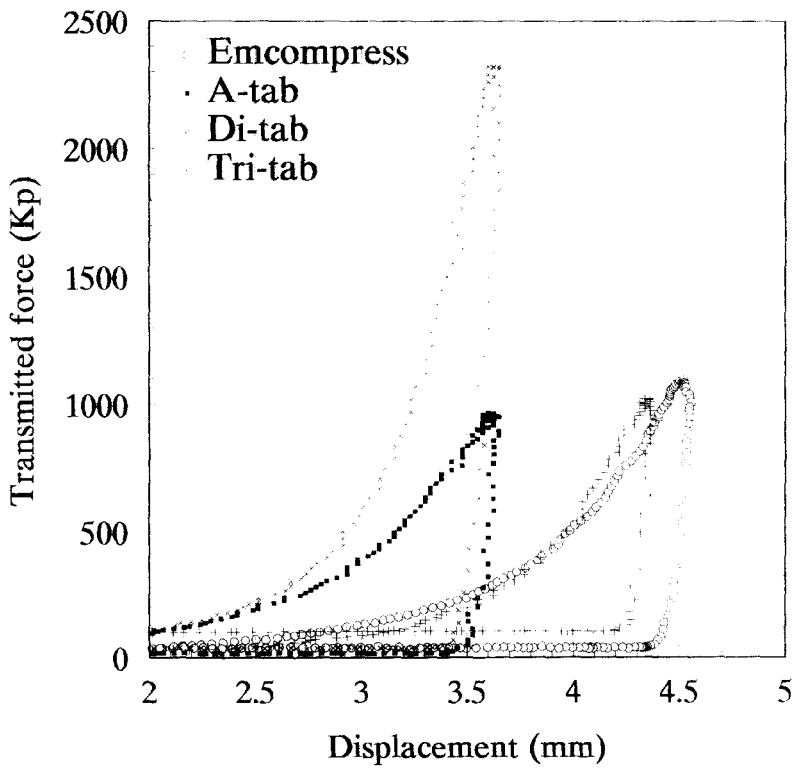

Fig. 1. Lower punch force-displacement curves.

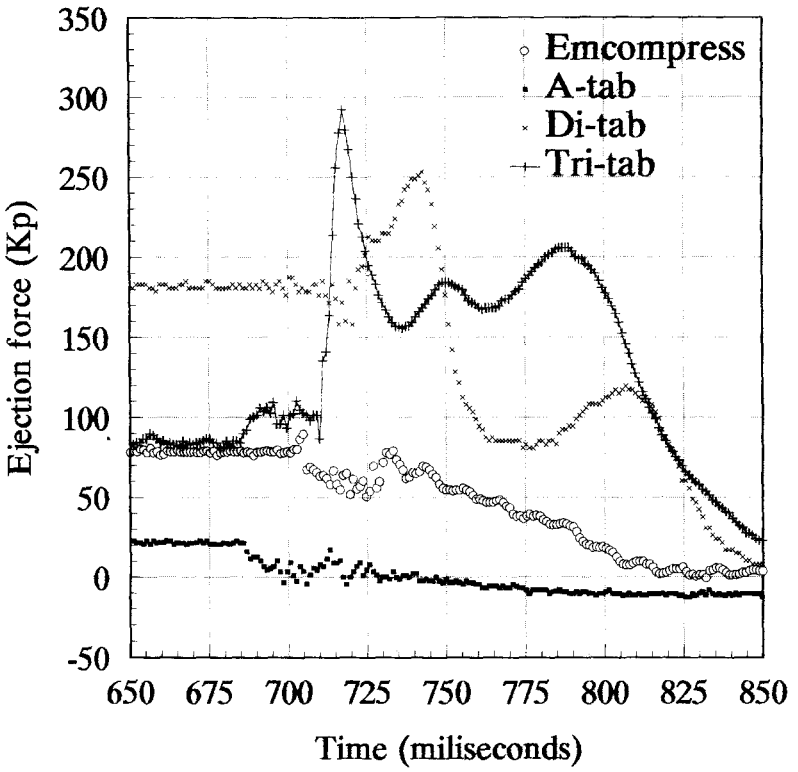

Fig. 2. Profiles of ejection force vs time.

rest of the calcium phosphate-based excipients, which may indicate the occurrence of minor rearrangement or plastic deformation from lower pressures than the other materials.

The different tests for lubricated tablets are listed in Table 6.

As expected from the flow characteristics of the excipients and the mixtures, low coefficients of weight variation were found. The tablets for all mixtures passed the test of weight uniformity (coefficient of tablet weight variation less than 1%). The mixture of Emcompress® with magnesium stearate exhibited the best flow characteristics and the lowest coefficient of tablet weight variation.

Tablets of Emcompress®, A-tab®, and Di-tab® demonstrated acceptable friability (less than 1%) (Table 6). In contrast, Tri-tab® exhibited unsatisfactory friability (48.82%). Finally, the disintegration time (Table 6) of lubricated tablets was, in

Table 5
Parameters of Heckel plot tablet-in-die method (average of five experiments ± S.D.)

Excipient	Da	Db′	D'_0	Py (MPa)	N	r	F
Emcompress®	0.512 ± 0.033	0.217 ± 0.009	0.475 ± 0.001	268.3 ± 13.4	40	0.9969	14 550
A-tab®	0.469 ± 0.013	0.161 ± 0.001	0.306 ± 0.009	273.7 ± 43.8	56	0.9981	14 124
Di-tab®	0.630 ± 0.006	0.251 ± 0.002	0.378 ± 0.008	342.6 ± 49.8	51	0.9965	6 949
Tri-tab®	0.531 ± 0.003	0.224 ± 0.002	0.305 ± 0.001	250.5 ± 23.4	57	0.9961	7 117

Table 6
Weight uniformity, thickness, friability and disintegration time of tablets prepared at 4 Kp crushing strength

Excipient	Weight uniformity (mg)	Coefficient of tablet variation	Thickness (mm)	Friability (%)	Disintegration time (min)
Emcompress®	298.6 ± 1.0	0.334	3.379 ± 0.006	0.64	21.46 ± 0.97
A-tab®	354.3 ± 1.8	0.508	4.423 ± 0.013	0.75	37.70 ± 1.28
Di-tab®	302.4 ± 1.2	0.397	3.346 ± 0.005	0.63	19.36 ± 1.27
Tri-tab®	342.3 ± 1.8	0.526	4.498 ± 0.083	48.42	13.75 ± 4.33

general, of appreciable length. The disintegration time of Tri-tab® was the shortest, being due to the insufficient consistency of the tablets with very high friability. The disintegration times of Emcompress® and Di-tab® showed non-significant differences.

4. Conclusions

The rheological properties of the new excipients A-, Di- and Tri-tab® were in general better than those of Emcompress®. In contrast, the mixture of Emcompress® with magnesium stearate exhibited the best flow characteristics and the lowest coefficient of tablet weight variation. Granulometry of the excipients demonstrated that Tri-tab® has a maximum mean diameter and a wide particle size distribution, while Emcompress® has a particle size distribution similar to that of Di-tab®.

The compressional characteristics demonstrated the values of the friction parameters to be insufficient in the case of Di- and Tri-tab® powders, therefore, lubrication would be a major factor in tableting with these excipients for direct compression. Totally different compressional behaviour of Di-tab was observed. In relation with the consolidation mechanisms, Emcompress® was the excipient showing lower brittle fracture and greater plasticity as compared with the other calcium phosphate-based excipients.

The disintegration times of lubricated tablets were, in general, quite long. The disintegration time of Tri-tab® was the shortest as a result of the insufficient consistency of the tablets with very high friability. The disintegration times of Emcompress® and Di-tab® showed non-significant differences. To summarize, it may be concluded that the new excipients A-, Di- and Tri-tab® do not improve on the tabletting properties of the classical calcium phosphate-based Emcompress® as a direct compression excipient.

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