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Dicalcium phosphate dihydrate and anhydrous dicalcium phosphate for direct compression: a comparative study

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Abstract

Dicalcium phosphate dihydrate (Emcompress) and anhydrous dicalcium phosphate (Anhydrous Emcompress) for direct compression were compared as regards particle size distribution and flow properties, which were found to be similar for the two products, and microporous structure and compression properties, which differed markedly. Specifically, intraparticular porosity and mean yield pressure of the anhydrous product were greater than for the dihydrate. Several properties of compacts of both products were also compared: compacts of the anhydrous phosphate disintegrated much more rapidly in distilled water than those of the dihydrate, which was attributed to the greater porosity of the former compacts.

Keywords: Dicalcium phosphate dihydrate; Anhydrous dicalcium phosphate; Direct compression; Flow properties; Compression properties; Microstructure

1. Introduction

Because of the excellent flow properties and low hygroscopicity and cost of dicalcium phosphate dihydrate (DCPD) for direct compression, this excipient is widely used (Carstensen and Ertell, 1990; Shangraw, 1991). However, one drawback to DCPD is its tendency to lose its hydration water (Rabatin et al., 1960; Dugleux and Sallier Dupin, 1967a; Ball and Casson, 1973), a process which is dependent on temperature and humidity (Dugleux and Sallier Dupin, 1967b; De Haan et al., 1990) and on the particle size of the DCPD (Landín et al., 1994b). Such dehydration can have serious effects on the chemical stability of some active principles or on the properties of solid dosage forms containing this excipient (Vila-Jato et al., 1985; Patel et al., 1988; Landín et al., 1994a).

The introduction of anhydrous dicalcium phosphate (ADCP) as a new excipient for direct compression should allow circumvention of the problems associated with the dihydrated product. In this work, we compare several characteristics of DCPD (Emcompress) and ADCP (Anhydrous Emcompress) products for direct compression.

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2. Materials and methods

2.1. Materials

Dicalcium phosphate dihydrate (Emcompress; batch no. 12D8; E. Mendell), anhydrous dicalcium phosphate (Anhydrous Emcompress; batch no. 1006; E. Mendell) and magnesium stearate B.P. (batch no. 832; C. Barcia).

2.2. Particle size analysis

Representative samples of the commercial DCPD and ADCP products were obtained by riffling in a Quantachrome Rotary Microriffler. Particle size distributions were then determined using a Coulter LS 100 Laser Scattering Particle Analyser. The results are expressed in terms of the mean volume diameter.

2.3. True density

True particle densities were determined in triplicate by helium pycnometry in a Quantachrome PY2 Micropycnometer.

2.4. Microporous structure

Microporous structures were determined using the following techniques.

Mercury intrusion porosimetry: Volumes of intruded mercury were determined on triplicate samples over the pressure interval 0.6–2000 lb/inch^2 using a Micromeritics 9305 Pore Sizer. The pore volume distribution (pores > 0.1 μm) was then evaluated from these data (Micromeritics, 1984).

Nitrogen adsorption: By means of the BET equation, specific surface areas were estimated from the results of triplicate nitrogen adsorption experiments, which were carried out at 77 K and at relative pressures of between 0.01 and 0.98 in a Micromeritics ASAP 2000 apparatus. Micropore volume distributions (pores < 0.1 μm) were determined from the nitrogen adsorption isotherms by the BJH method (Stanley-Wood, 1983).

Total porosity (%) was calculated from the sum of the values obtained by each of the above methods (Stanley-Wood, 1983).

2.5. Flow properties

Bulk densities: Tapped bulk densities were determined in triplicate in a Hosokawa PT-E Powder Tester, tapping at 50 taps/min for 20 min. Compressibilities (%) were then calculated from the bulk densities (Thomson, 1984).

Shear strength: Measurements were carried out on an IPT RO-200 automatic apparatus equipped with a rotational split-level shear cell. Duplicate samples of DCPD and ADCP were subjected to four loads of consolidation, thus allowing obtaining of a family of four yield loci – each defined by five normal stresses – with final stress corresponding to 50, 100, 150 or 250 g/cm^2. Mohr circle analysis of these loci enabled estimation of the unconfined yield stress (f_c) and the major principal consolidating stress (σ_1) (Brown and Richards, 1970). Regression of σ_1 on f_c gives a straight line whose slope is the inverse of the flow factor (Svarovsky, 1987a).

2.6. Compression properties

Prior to compression, each product was mixed with 1% (w/w) magnesium stearate (5 min at 30 rpm in a Túrbula T2C mixer). Triplicate subsamples of each material were then compressed in a Korsch EKO excentric press equipped with flat-faced 9 mm punches and a data handling system (Martínez-Pacheco et al., 1985). Mean yield pressures under load were determined using Heckel plots of the data for compression force-displacement cycles (Humbert-Droz et al., 1982).

2.7. Preparation and characterization of compacts

Using the apparatus described above and applying maximum compaction pressures of 80 or 160 MPa, two formulations in 350 mg compacts were prepared from each product. Each formulation was subjected to the following tests.

Microporous structure: Samples were evaluated as described for the uncompressed products.

Tensile strength: The crushing strength of six compacts was determined using an Erweka TB 2A apparatus; mean tensile strengths were then calculated from these results and the dimensions

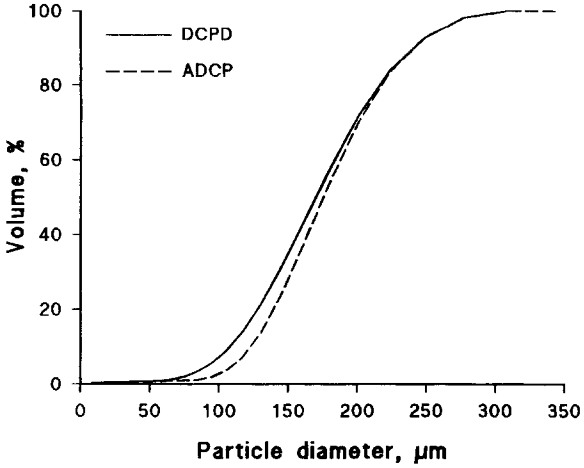

Fig. 1. Particle size distributions (determined by laser scattering) for the dicalcium phosphate dihydrate (DCPD) and anhydrous dicalcium phosphate (ADCP) samples studied.

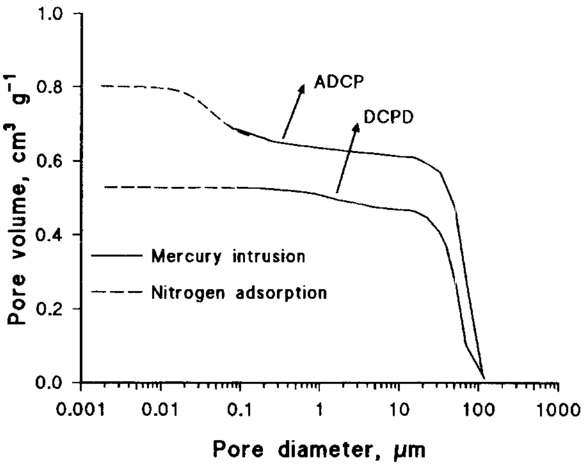

Fig. 2. Pore volume distributions for the dicalcium phosphate dihydrate (DCPD) and anhydrous dicalcium phosphate (ADCP) samples studied.

of each compact, which were measured using a Mitutoyo digital micrometer (Fell and Newton, 1970).

Disintegration time: Measurements were carried out using a Turu Grau apparatus, which conforms to the specifications exacted in USP XXII. Mean values were calculated from the disintegration times of six compacts in distilled water (as attacking medium).

3. Results and discussion

For the two phosphates studied, Fig. 1 shows the cumulative particle size distribution curves, illustrating that their particle size distributions are very similar. This is confirmed by the similar mean volume diameters obtained for the two products (Table 1).

The magnitude of the difference between the true densities (Table 1) indicates that this difference derives from the absence and presence of hydration water in ADCP and DCPD, respectively.

Mercury intrusion and nitrogen adsorption experiments (Fig. 2) clearly show that the anhydrous phosphate has the greater intraparticular porosity. In fact, the micropore volume (pores < 0.1 μm) of the anhydrous phosphate is some 70-times greater than that of the dihydrated com-

Table 1
Characteristic properties of dicalcium phosphate dihydrate (DCPD) and anhydrous dicalcium phosphate (ADCP)

Parameter	DCPD	ADCP
Mean particle size (μm)	172.7	174.9
True density (g cm^{-3})	2.312 (0.033)	2.959 (0.019)
Specific surface area (m^2 g^{-1})	0.812 (0.023)	17.567 (0.331)
Micropore volume (pores < 0.1 μm) (cm^3 g^{-1})	0.0019 (0.0001)	0.1284 (0.0014)
Total porosity (%)	55.87 (0.75)	68.49 (0.34)
Compressibility (%)	15.89 (1.07)	16.59 (1.77)
Flow factor	9.18 (0.50)	8.18 (0.49)
Mean yield pressure (MPa)	219.1 (19.7)	547.9 (36.3)

Mean values are followed by standard deviations in parentheses.

pound (Table 1), thus accounting for the very much greater specific surface area measured for ADCP.

The anhydrous phosphate also has slightly greater compressibility and lower fluidity than the dihydrated product (Table 1), although for both phosphates these parameters indicated that they are free flowing (Svarovsky, 1987a). The slightly superior flow properties of the dihydrated product may be attributable to differences in the effective particle densities of the two products: due to its greater intraparticular porosity, the anhydrous product would be expected to have slightly lower effective particle density, and consequently greater compressibility (Svarovsky, 1987b).

The mean yield pressures for the two products (Table 1) indicate that for both the predominant consolidation mechanism was particular fragmentation (Humbert-Droz et al., 1983). The higher mean yield pressure obtained for ADCP is possibly a reflection of the different microporous characteristics of the compacted products. This is suggested by comparison of Fig. 2 and 3, respectively, showing the cumulative pore volume distribution curves for the uncompressed and compressed products, which indicates that the micropore volume measured for the anhydrous phosphate is entirely maintained in both its compacted formulations (Table 2). The differences between the specific surface areas measured for the compacts obtained at 80 MPa and those obtained at 160 MPa (i.e., an approx. 10% increase for the dihydrate, and a smaller 3% increase for the anhydrous phosphate; Table 2) are also in keeping with this hypothesis.

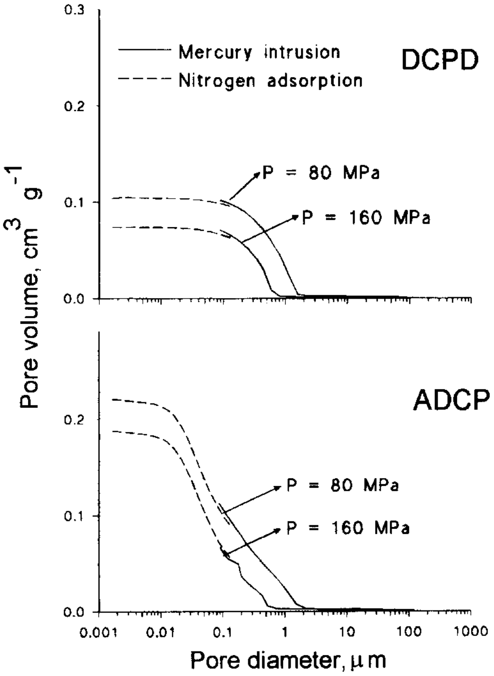

Fig. 3. Pore volume distributions for compacts of dicalcium phosphate dihydrate (DCPD) and anhydrous dicalcium phosphate (ADCP), prepared using maximum compaction pressures (P) of 80 and 160 MPa.

Table 2 includes the mean tensile strengths of the two formulations of each product. Underlying the clear difference between the tensile strengths of compacts formed at 80 MPa and those formed at 160 MPa, a slight superiority of the DCPD

Table 2

Characteristic properties of compacts of dicalcium phosphate dihydrate (DCPD) and anhydrous dicalcium phosphate (ADCP) prepared using maximum compaction pressures of 80 or 160 MPa

Parameter	DCPD		ADCP	
	80 MPa	160 MPa	80 MPa	160 MPa
Specific surface area ($m^2\ g^{-1}$)	1.187 (0.043)	1.305 (0.021)	18.250 (0.543)	18.801 (0.262)
Micropore volume (pores < 0.1 μm) ($cm^3\ g^{-1}$)	0.0081 (0.0005)	0.0102 (0.0003)	0.1272 (0.0037)	0.1236 (0.0061)
Total porosity (%)	20.57 (1.07)	14.37 (1.40)	41.53 (0.47)	35.96 (0.77)
Tensile strength (MPa)	0.63 (0.06)	1.31 (0.05)	0.47 (0.04)	1.07 (0.08)
Disintegration time (min)	127.0 (37.6)	1208.7 (291.2)	45.0 (6.4)	73.0 (6.2)

Mean values are followed by standard deviations in parentheses.

product is apparent, as would be expected given the differences observed in the microporous structures and mean yield pressures of the two products.

There are marked differences between the disintegration times of compacts prepared from anhydrous dicalcium phosphates and those prepared from the dihydrated product (Table 2). The faster disintegration of ADCP compacts is doubtless due to their greater total porosity, particularly the sizeable contribution to this from micropores (pores < 0.1 μm), which, as stated above, are maintained in these compacts.

4. Conclusions

The anhydrous and dihydrated dicalcium phosphate products for direct compression have similar particle size distributions and flow properties. Nevertheless, their compression properties are markedly different, giving rise to a lower mean yield pressure for the dihydrated phosphate. Furthermore, the greater intraparticular porosity of the anhydrous phosphate, in particular the contribution due to micropores (pores < 0.1 μm), causes compacts of this product to disintegrate much more rapidly in distilled water than those of the dihydrated phosphate.

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References

Ball, M.C. and Casson, M.J., The hydration of calcium hydrogen phosphate dihydrate. *J. Chem. Soc. Dalton Trans.*, 1 (1973) 34–37.

Brown, R.L. and Richards, J.C., Essays on the packing and flow of powders and bulk solids. *Principles of Powder Mechanics*, Pergamon, London, 1970, pp. 40–57.

Carstensen, J.T. and Ertell, C., Physical and chemical properties of calcium phosphates for solid state pharmaceutical formulations. *Drug Dev. Ind. Pharm.*, 16 (1990) 1121–1133.

De Haan, P., Kronn, C. and Sam, A.P., The composition and stabilization of the tablet excipient calcium hydrogen phosphate dihydrate. *Drug Dev. Ind. Pharm.*, 16 (1990) 2031–2055.

Dugleux, P. and Sallier Dupin, A., Contribution à l'étude cinétique de la déshydratation du phosphate bicalcique: II. Déshydratation de $CaHPO_4 \cdot 2H_2O$ en ambiance sèche ou légèrement humide. *Bull. Soc. Chim.*, 3 (1967a) 973–977.

Dugleux, P. and Sallier Dupin, A., Contribution à l'étude cinétique de la déshydratation du phosphate bicalcique: III. Interprétation des résultats, ébauche du mécanisme réactionnel. *Bull. Soc. Chim.*, 3 (1967b) 978–982.

Fell, J.T. and Newton, J.M., Determination of tablet strength by diametral-compression test. *J. Pharm. Sci.*, 59 (1970) 688–691.

Humbert-Droz, P., Mordier, D. and Doelker, E., Densification behaviour of powder mixtures. *Acta Pharm. Technol.*, 29 (1983) 69–73.

Humbert-Droz, P., Mordier, D. and Doelker, E., Rapid method of determination of compression behaviour for preformulation studies. *Pharm. Acta Helv.*, 57 (1982) 136–143.

Landín, M., Pérez-Marcos, B., Casalderrey, M., Martínez-Pacheco, R., Gómez-Amoza, J.L., Souto, C., Concheiro, A. and Rowe, R.C., Chemical stability of acetylsalicylic acid in tablets prepared with different commercial brands of dicalcium phosphate dihydrate. *Int. J. Pharm.*, 107 (1994a) 247–249.

Landín, M., Rowe, R.C. and York, P., Particle size effects on the dehydration of dicalcium phosphate dihydrate powders. *Int. J. Pharm.*, 104 (1994b) 271–275.

Martínez-Pacheco, R., Gómez-Amoza, J.L. and Vila-Jato, J.L., Diseño de un sistema de registro de presión en máquinas de comprimir excéntricas. *Cienc. Ind. Farm.*, 4 (1985) 207–211.

Micromeritics Instruction Manual, Pore Size 9305, Micromeritics, Norcross, 1984.

Patel, N.K., Patel, I.J., Cutie, A.J., Wadke, D.A., Monkhouse, D.C. and Reier, G.E., The effect of selected direct compression excipients on the stability of aspirin as a model hydrolyzable drug. *Drug Dev. Ind. Pharm.*, 14 (1988) 77–98.

Rabatin, J.G., Gale, R.H. and Newkirk, A.E., The mechanism and kinetics of the dehydration of calcium hydrogen phosphate dihydrate. *J. Phys. Chem.*, 64 (1960) 491–493.

Shangraw, R.F., Direct compression in tableting. In Swarbrick, J. and Boylan, J.C. (Eds), *Encyclopedia of Pharmaceutical Technology*, Vol. 4, Dekker, New York, 1991, pp. 85–106.

Stanley-Wood, N.G., Particle characterization by size, shape and surface for contacted particles. *Enlargement and compaction of particulate solids*, Butterworths, London, 1983, pp. 43–119.

Svarovsky, L., Methods of measuring the physical properties of bulk powders. *Powder Testing Guide*, Elsevier, London, 1987a, p. 36.

Svarovsky, L., Methods of measuring the physical properties of bulk powders. *Powder Testing Guide*, Elsevier, London, 1987b, p. 16.

Thomson, F.M., Storage of particulate solids. In Fayed, M.E. and Otten, L. (Eds), *Handbook of Powder Science and Technology*, Van Nostrand Reinhold, New York, 1984, pp. 365–457.

Vila-Jato, J.L., Concheiro, A. and Torres, D., Influence of storage conditions on the characteristics of digoxin-Emcompress tablets. *STP Pharm.*, 1 (1985) 194–200.