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Note

Particle size effects on the dehydration of dicalcium phosphate dihydrate powders

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Abstract

The particle size of dicalcium phosphate dihydrate (DCPD) has a strong influence on its dehydration behaviour, specifically the weight loss in the first stage of dehydration. This weight loss has been found to be inversely proportional to the mean particle size of the samples. Mean particle size may be a useful parameter in predicting the dehydration behaviour of DCPD and is clearly a contributing factor in explaining batch and source variation.

Key words: Dicalcium phosphate dihydrate; Dehydration behavior; Particle size

Dicalcium phosphate dihydrate (DCPD) is a commonly used filler in solid dosage forms. The dehydration of DCPD, which is relevant to its pharmaceutical use, has been reported to be complex and dependent on both temperature and water-vapour pressure (Dugleux and Sallier Dupin, 1967a,b; De Haan et al., 1990). In dry air, the dehydration process of DCPD powders occurs in two steps (Boullé and Jolibois, 1948) and differences in the relative proportions of these steps in several sources of DCPD have been related to the characteristics of the manufacturing process (Boullé et al., 1955; Landín et al., 1994). Particle properties of DCPDs, such as crystal structure, particle size and shape and particle structure of aggregates, depend heavily on the conditions prevailing during particle formation by precipitation especially temperature and precipitation rate (Boullé and Dupont, 1955). In this work, the particle size dependence of the dehydration process has been quantified.

The DCPD powder studied was a sample from Kyowa (Japan). Optical examination of the material showed the particles to be crystalline with plate-like habit over particle sizes up to 200 μm.

Seven particle size fractions were fractionated using an Alpine Multiplex Zig Zag A100 MZR classifier. Cut size was in the range 5–75 μm.

Particle size distributions were determined using a Malvern 2600 laser scattering particle size

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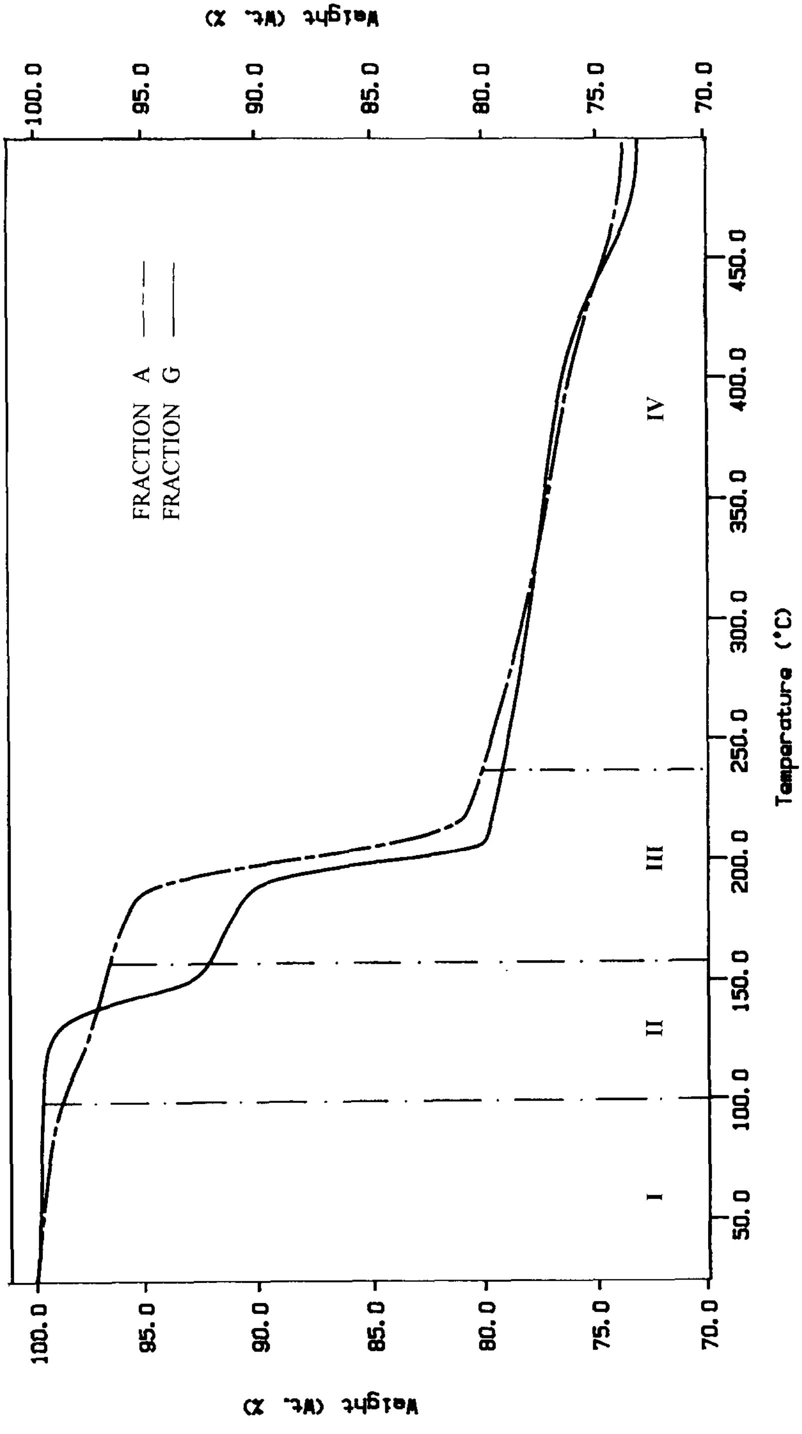

Fig. 1. TGA curves of the two DCPD fractions studied.

Table 1
Geometric mean particle size and specific areas of the DCPD fractions studied (standard deviations in parentheses)

Fraction	Geometric mean particle size (μm)	Surface area (m^2/g)
A	8.10 (3.77)	5.33 (0.01)
B	15.48 (11.77)	1.49 (0.01)
C	25.29 (18.69)	0.78 (0.00)
D	30.72 (21.62)	0.63 (4×10^{-4})
E	36.34 (26.09)	0.53 (8×10^{-3})
F	47.68 (42.75)	0.36 (8×10^{-4})
G	63.95 (41.05)	-

analyser. Particle size distributions were relatively broad, which may be related to the plate like particle shape: the distributions were significantly log normally distributed ($0.97 < r^2 < 0.99$; $\alpha < 0.01$) and were determined using the geometric mean and standard deviation (Table 1) (Allen, 1990).

Surface areas (Table 1) were determined in a Micromeritics Flowsorb II 2300 using the BET method of nitrogen adsorption after degassing samples under vacuum at 60°C for 24 h.

Thermogravimetric analysis (TGA) was carried out in a Perkin-Elmer TGA 7 Analyzer linked to a Perkin-Elmer 7700 computer via the TAC7 microprocessor controller. Samples (3–3.5 mg) from each particle size range were heated from 25 to 500°C at rate of 10°C/min under a dry nitrogen gas current.

For all fractions, weight loss was shown by TGA (Fig. 1) to occur in four stages. The first step corresponds to a small weight loss below 100°C which is attributed to the removal of physically adsorbed surface moisture (0.5–0.7% for this product) (Dugleux and Sallier Dupin, 1967a).

The second and third steps (II and III, Fig. 1) are associated with loss of water of hydration and formation of anhydrous dicalcium phosphate ($CaHPO_4 \cdot 2H_2O \rightarrow CaHPO_4 + 2H_2O$; 2 mol of water of crystallisation accounts for a 20.9% w/w weight loss). Ignition at 500°C gave an additional weight loss (IV, Fig. 1) to produce pyrophosphate ($CaHPO_4 \rightarrow Ca_2P_2O_7 + H_2O$; 5.23%).

TGA data (Table 2) show that below 100°C water loss decreased with an increase in particle size. For fraction A, with the smallest mean particle size, a loss of 1.18% is recorded. This is higher than the assigned level of surface moisture, indicating partial dehydration below 100°C. Moreover, there is a close correlation between water loss below 100°C and the specific surface of DCPD fractions ($r^2 = 0.9971$, df = 5, $\alpha < 0.01$). These results are consistent with the mechanism proposed by Dugleux and Sallier Dupin (1967a,b) that the dehydration process in this preliminary stage (step I) is a superficial phenomenon.

In all fractions, loss of water of crystallisation occurred in two steps – II and III – (at approx. 145 and 190°C), but the relative proportion of water removed at each step of the process varied significantly with particle size. It is interesting to note that for the smaller sized fractions A and B total weight loss for these two steps is less than the stoichiometric value of 20.9% which corroborates the previous comments. As particle size decreases (Fig. 2) and specific surface area increases, the first dehydration step contributes less to the overall process. Loss of water in the second

Table 2
DCPD characteristics obtained from TGA curves (standard deviations in parentheses)

Fraction	Weight loss (% w/w)			
	I (below 100°C)	II (100–165°C)	III (165–240°C)	IV (240–500°C)
A	1.18 (0.04)	2.33 (0.02)	16.43 (0.04)	6.27 (0.05)
B	0.47 (0.05)	4.92 (0.07)	15.46 (0.06)	5.87 (0.04)
C	0.40 (0.03)	6.76 (0.09)	13.86 (0.05)	5.93 (0.02)
D	0.43 (0.04)	7.39 (0.02)	13.26 (0.10)	5.90 (0.06)
E	0.33 (0.04)	7.60 (0.05)	12.99 (0.03)	5.89 (0.06)
F	0.29 (0.02)	7.71 (0.06)	12.90 (0.04)	5.98 (0.02)
G	0.24 (0.10)	7.96 (0.07)	12.60 (0.04)	5.97 (0.11)

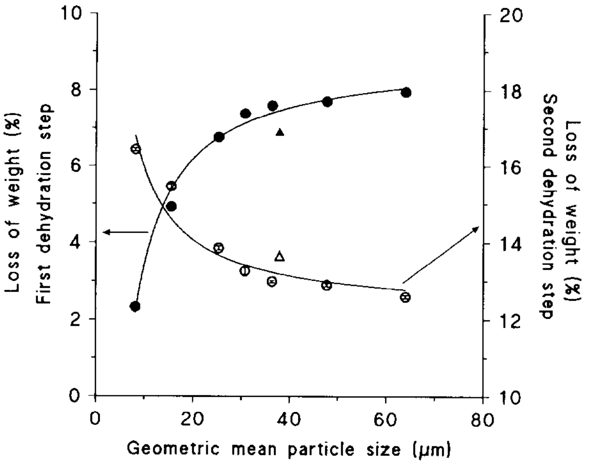

Fig. 2. Loss of weight in the first dehydration step (left) and second dehydration step (right) vs mean particle size of DCPD fractions. (●,○) Fractions of Kyowa; (▲,△) Kyowa as supplied.

dehydration step is limited by the amount lost previously.

In order to explain the differences in water loss in the first step between different sized fractions it is necessary to consider that loss of water of DCPD is an autocatalytic phenomenon (Dugleux and Sallier Dupin, 1967a) and dehydration of DCPD is a diffusion-controlled reaction (Ball and Casson, 1973). It is possible that on heating, higher internal water vapour pressures are generated in the larger crystals promoting the catalytic reaction. Such a process would therefore be reduced if the initial rate of water removal by the flow of dry nitrogen was rapid, as presumably occurs in fractions with smaller particle size and large surface area.

Loss of weight in the first step of dehydration vs mean particle size fits the following relationship:

$$\%\ \text{loss of water} = A + B(1/d) \qquad (1)$$

where A and B are constants and d denotes the mean particle size of the DCPD fraction. Regression analysis (Table 3) shows a good correlation with the regression coefficient $r^2 = 0.9860$ (df = 5;$\alpha < 0.01$).

From Eq. 1, it is possible to predict dehydration behaviour in dry air from knowledge of the mean particle size of the DCPD powder. In fact, the dehydration process of the unfractionated sample (Fig. 2), which has a mean particle size of 32 µm, occurred in two steps. In the first step, loss of weight was 6.9% w/w, very close to the value of 7.2% predicted from Eq. 1.

Table 3
Results of regression analysis for Eq. 1

		t
A	8.91 ± 0.17	53.02
B	-54.47 ± 2.90	−18.79

The equivalence in weight loss in the first stage of dehydration between both unfractionated and fractionated samples of the same mean particle size and the relationship between this weight loss and the reciprocal of mean particle size (Eq. 1) are analogous to those seen in unfractionated and fractionated polymers for both mechanical properties (Flory, 1945; Sookne and Harris, 1945; Ogawa 1992) and, more recently, heats of hydration (Rowe and McKillop, 1993). This suggests that results observed in this study for any sample blend ΔW_{blend} can be expressed mathematically by the expression:

$$\Delta W_{\text{blend}} = \frac{\sum w_i \Delta W_i}{\sum w_i} \qquad (2)$$

where w_i is the weight proportion of a sample with a weight loss in the first stage of dehydration of ΔW_i. This expression should allow the production of any sample blend from a knowledge of the weight proportion of the individual components. This hypothesis has been tested by investigating binary mixtures of two fractions B and F (25:75; 50:50; 75:25% w/w). For all binary blends there

Table 4
Comparison of observed and predicted (Eq. 2) values of weight loss in the first stage of dehydration for binary blends

Blend [a]	(% w/w) Weight loss during first dehydration stage	
	Observed	Predicted
25–75	7.01	7.11
50–50	6.24	6.31
75–25	5.61	5.61

[a] w/w ratio for fractions B and F.

was a close correlation between the observed weight loss in the first stage of dehydration and predicted values from Eq. 2 (Table 4). A consequence of this analysis is that every individual crystal should have a different weight loss during the first stage of dehydration proportional to the reciprocal of its diameter, i.e., the weight loss is in some way related to the packing of molecules in the unit cell. This aspect will be examined in a future publication.

In conclusion, it can be seen that particle size has a strong influence on dehydration behaviour, but not the specific surface area as might be expected. Mean particle size may be a useful parameter in predicting characteristics of the dehydration process of DCPD and is clearly a contributing factor in explaining the inter-lot and inter-manufacturer variability of the DCPD powder (Landín et al., 1994).

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2. References

Allen, T., *Particle Size Measurements*, Chapman and Hall, London, 1990, pp. 156–160.

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

Boullé, M.A. and Dupont, M.M., Sur la déshydratation du phosphate bicalcique. *C.R. Acad. Sci.*, 240 (1955) 860–862.

Boullé, M.A. and Jolibois, M.P., Sur la déshydratation du phosphate bicalcique. *C.R. Acad. Sci.*, 226 (1948) 1617–1619.

De Haan, P., Kronn, C. and Sam, A.P., Decomposition 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.

Flory, P.J., Tensile strength in relation to molecular weight of high polymers. *J. Am. Chem. Soc.*, 67 (1945) 2048–2050.

Landín, M., Martínez-Pacheco, R., Gómez-Amoza, J.L., Souto, C., Concheiro, A. and Rowe, R.C., The effect of country of origin on the properties of dicalcium phosphate dihydrate powder. *Int. J. Pharm.*, 103 (1994) 9–18.

Ogawa, T., Effects of molecular weight on mechanical properties of polypropylene. *J. Appl. Polym. Sci.*, 44 (1992) 1869–1871.

Rowe, R.C. and McKillop, A.G., Molecular weight dependence of the heats of hydration of some oligomeric ethylene oxides and their methoxyl derivatives. *J. Appl. Polym. Sci.*, 45 (1993) In press.

Sookne, A.M. and Harris, M., Polymolecularity and mechanical properties of cellulose acetate. *Ind. Eng. Chem.*, 37 (1945) 478–482.