International Journal of Pharmaceutics, 25 (1985) 207-215
Elsevier

IJP 00850

Compression characteristics of basic tricalcium phosphate ($Ca_3(PO_4)_2$, $Ca(OH)_2$)

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(Received July 27th, 1983)
(Modified version received and accepted February 15th, 1985)

Key words: compression – tricalcium phosphate – Heckel equation – density – tablets – dicalcium phosphate dihydrate

Summary

It is shown that tricalcium phosphate obeys the Heckel equation only if a particle density of 1.92 g/cm^3 (rather than the true density of 3.1 g/cm^3) is used to determine the relative density of compacts. It is shown by comparing mercury intrusion porosimetry data with nitrogen adsorption data, that a large portion of the solid has pores of diameters of less than 60 Å. It would appear that this part of the pore space is not compressible in conventional pressure ranges, and that it should not be considered part of the Heckel pore space. It is shown by hysteresis loops that (in as much as simple interpretations are permissible) there is a substantial amount of ink-bottle pores, and that both neck and cavity volumes decrease in a logical fashion with increased applied pressure.

Introduction

Basic tricalcium phosphate[1] ($3Ca_3(PO_4)_2$, $Ca(OH)_2$) which in the following will simply be denoted tricalcium phosphate, is a good direct compression excipient[1], and is marketed as such. It is non-hygroscopic below 50% relative humidity at 25°C and does not give up water of hydration in dry atmospheres (since it has no water of hydration).

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[1] Tri-Tab, Stauffer Chemicals, Elmsford, NY.

Compressibility behavior is conveniently characterized by Heckel plots (Heckel, 1961). Here the relative density (R) is conventionally related to applied pressure, Π (kN), by the equation:

$$\ln(1 - R) = k \cdot \Pi + b \qquad (1)$$

where k and b are constants. The relative density is obtained as the ratio between the apparent density, ρ' (g/cm^3), of the compact and the particle density, ρ^* (g/cm^3), i.e.

$$R = \rho'/\rho^* \qquad (2)$$

It is the intent of this article to report on compression of tricalcium phosphate by this type of equation, and certain observed anomalies.

Materials and Methods

The material was used as received from the supplier [1]. This tricalcium phosphate has (characteristically and specifically) a particle size distribution, where 18% by weight is 30/40 mesh (420–590 μm), 50% are 40/60 mesh (250–420 μm), 23% is 60/80 mesh (170–250 μm) and the remainder is finer than 80 mesh.

To make the compact, 0.5 g of material was compressed on a motorized hydraulic press [2]. The speed and time-of-dwell of the punch is controlled so that the application of force is carried out in 20 s, followed by a 5 s dwell-time. One cm diameter flat-faced punches (without bevel) were used; the forces of compression used are shown in Table 1.

To obtain the apparent density of the tablets, their dimensions at several compression pressures were determined. These are listed in Table 2. The particle density can be calculated from this as:

$$\rho_1' = W \cdot \{V - (We)\}^{-1} \qquad (3)$$

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[2] Fred Carver, Menomonee Falls, WI, U.S.A.; Press with motorized unit.

TABLE 1

HECKEL PLOT PARAMETERS FOR TRICALCIUM PHOSPHATE

Load (kN)	Apparent density [a] (ρ'g/cm^3)	$\ln\{1-(\rho'/3.1)\}$	$\ln\{1-(\rho'/1.92)\}$
4.5	1.384	−0.59	−1.27
8.9	1.475	−0.646	−1.46
13.3	1.571	−0.707	−1.70
17.8	1.589	−0.719	−1.76
22.2	1.659	−0.766	−2.00
35.6	1.776	−0.851	−2.59

[a] Tablets are flat-faced without bevel, with a diameter of 1.04 cm.

TABLE 2

PORE AND DIMENSIONAL DATA AT VARIOUS LOAD

	Load at which tablet was made (kN):					
	4.5	8.9	13.3	17.8	22.8	35.6
Height, (h, cm) **	0.492	0.401	0.373	0.366	0.353	0.330
Weight, W (g)	0.499	0.498	0.498	0.496	0.498	0.499
Volume V (cm^3) *	0.362	0.338	0.316	0.311	0.301	0.282
Porosity, e (cm^3/g)	0.0316	0.0278	0.0245		0.0237	
V – (We) (cm^3)	0.346	0.324	0.304		0.289	
W/(V – {We}) = ρ_1'	1.44	1.54	1.64		1.72	
ρ_2' from penetrometry	1.48	1.60	1.69		1.79	
Volume–diameter mean pore diameter (μm)	0.018	0.016	0.014		0.012	
Surface area (m^2/g)	7.1	7.0	6.8		6.7	

* Only two figures are fully significant, but the extra digit is shown for calculation clarity, e.g. of apparent density figures.

** The diameter is 1.04 cm in all cases.

where ρ_1' is the density, W is the tablet mass in grams, e is the pore volume in cm^3/g and V is the tablet volume (cm^3).

The density of the tricalcium phosphate was obtained by simple pycnometry (Carstensen, 1977) using water and methanol as pycnometer fluids. The values obtained were 1.90–1.92 g/cm^3 which is considerably less than the literature value [3] of 3.1 g/cm^3. When the pycnometer is placed in an ultrasonic bath, then the samples become turbid, and the density obtained is now the theoretical (3.1 g/cm^3).

The tablets were tested in a mercury porosimeter [4] using pressures up to 30,000 psi. Nitrogen adsorption was used to obtain surface areas.

For comparison, similar studies were carried out with dibasic calcium phosphate dihydrate [5]. This will be referred to simply as dicalcium phosphate in the following, and it is, as known, a well-established direct compression excipient.

Results and Discussion

When the data from columns 1 and 3 in Table 1 are plotted (as in Fig. 1) it is apparent that the Heckel plot fails to be linear. It would appear from the pycnometric behavior of the tricalcium phosphate, that the particles have occluded void space which is not accessible to liquids. This space might also be unavailable to the compression process in the range of pressures tested. If the value of 1.92 g/cm^3 obtained by simple pycnometry is used to obtain relative densities, R, then the data in column 4 of Table 1, and the *linear* plot in Fig. 2 result.

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[3] Tri-Tab, a new direct compression excipient, Stauffer Chemicals, Elmsford, NY, U.S.A. Bulletin B-11457/6-82.

[4] Mercury Intrusion Porosimeter, Model 9300, Micromeritics, Norcross, GA 30093, U.S.A.

[5] Di-Tab, unmilled dicalcium phosphate dihydrate, USP/FCC in Direct Compression Tableting, Stauffer Chemicals, Elmsford, NY, U.S.A.

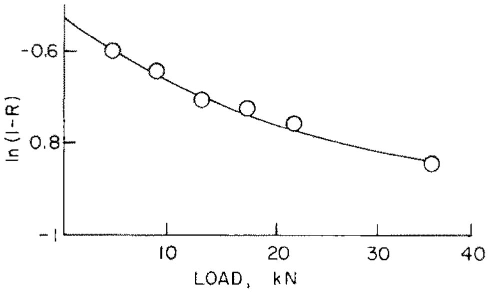

Fig. 1. Heckel plot of tricalcium phosphate, using the true density (3.1 g/cm^3) for particle density.

There is, of course, the possibility that pores could be occluded at lower pressures and still be "opened up" when higher pressures are applied. To obtain information in this regard, mercury porosimetry was performed, and the obtained intrusion profiles are shown in Fig. 3.

The data obtained by geometric dimensions of the tablets and those obtained by pycnometry are consistent with one another. The porosity values, e, in Table 2 are those obtained by porosimetry, i.e. they do not include the "occluded" pore space. Hence the particle density, ρ', can be obtained from the tablet dimensions using Eqn. 3. These values should correspond with the particle density obtained directly from porosimetry. It is seen in Table 2 that the values are quite close.

It should be noted that the surface area (A; cm^2/g) can be calculated from the porosity data and when this is done (assuming a cylindrical pore model (a bundle of tubes model), as described by Dullen, 1979), then a value of A of 7 m^2/g is found. This is an order of magnitude less than the value (77 m^2/g) reported in literature [3] (a value which has been confirmed, experimentally, in this study). It is realized that

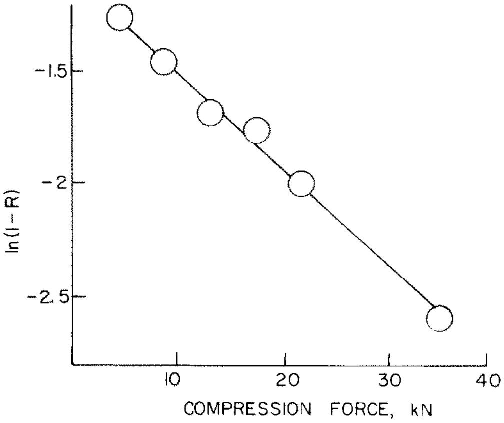

Fig. 2. Heckel plot of tricalcium phosphate, using the unadjusted pycnometric density (1.92 g/cm^3) as particle density.

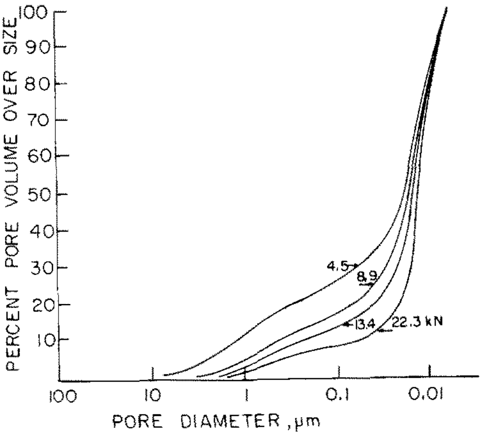

Fig. 3. Mercury intrusion porosimetry curves for tablets made at different compression forces. Punch diameter 1.04 cm.

the tube model gives rise to underestimates, but is nevertheless likely, in particular considering the linearization shown in Fig. 2, and the fact that the wet pycnometric density is low, that there is the presence of "occluded" pores which are not accessible to liquids, but are accessible to nitrogen. Pores smaller than a critical size dictated by this occlusion, will behave as if they are not a part of the Heckel pore space. This is not the case with dicalcium phosphate, which will be discussed at a later point.

Fig. 5.

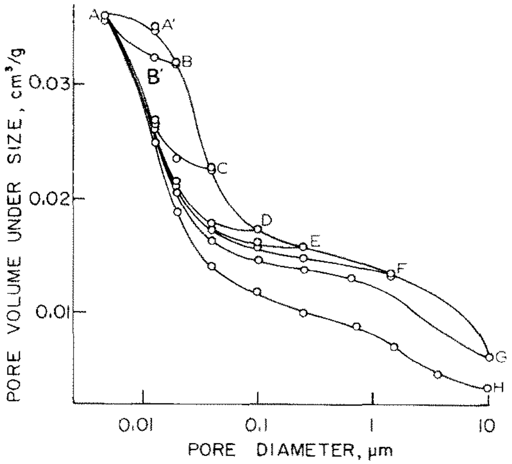

Fig. 4.

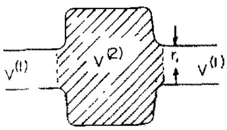

Fig. 4. Schematic representation of an ink bottle pore.

Fig. 5. Hysteresis loops of dicalcium phosphate tablet compressed at a compression force of 2.7 kN. Flat faced punch of 1.04 cm diameter.

TABLE 3

HYSTERESIS ANALYSIS OF TRICALCIUM PHOSPHATE

Compression force (kN)	100 × neck pore volume $V^{(1)}$ (ml/g)	100 × cavity pore volume, $V^{(2)}$ (ml/g)	100 × retained volume (ml/g)	100 × total volume (ml/g)
2.7	1.21	1.88	0.27	3.36
6.7	0.48	1.36	0.62	2.46
13.3	0.30	1.39	0.50	2.19
17.8	0.21	0.56	0.40	1.18
22.2	0.18	0.44	0.44	1.06
31.1	0.14	0.67	0.31	1.12
44.5			0.27	0.68

If the above holds true, then there should be the occurrence of ink-bottle pores (Dullien, 1979); these are of the type shown in Fig. 4. A possible means of obtaining information of this pore structure has been suggested by Reverberi et al. (1966). The general principle is that it takes a given threshold pressure, P_1, (which corresponds to the radius, r_1, in Fig. 4) for the ink-well to be filled. This will give the appearance in the porosity curve as if the total volume $V^{(1)} + V^{(2)}$ in Fig. 4 belonged to the pore space with radius, r_1. Fig. 5 shows the treatment of the hysteresis loop. Fig. 5 shows the pore intrusion of mercury from low pressure at H (where the pore radius is large and the volume over size is small) up to A at high pressure (where the pore radius is small and the volume over size is large). If the pressure is reduced, then the curve A-A′-B results. Increasing the pressure returns the system to B via B′. This process has been repeated at 5 points (C,D,E,F and G) to produce the curve in Fig. 5.

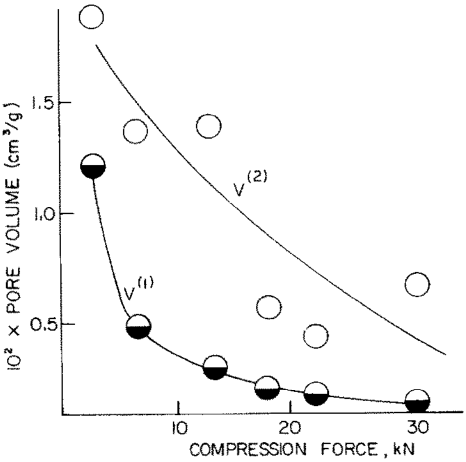

Fig. 6. Plot of neck pore volume, $V^{(1)}$, and cavity pore volume $V^{(2)}$, as a function of compression force.

Fig. 7.

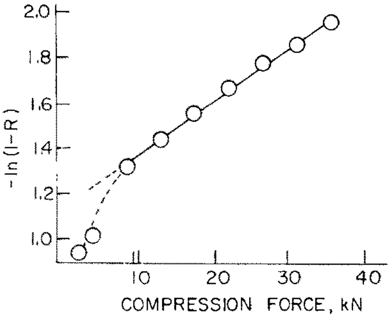

Fig. 7. Heckel plot for dicalcium phosphate dihydrate.

Fig. 8.

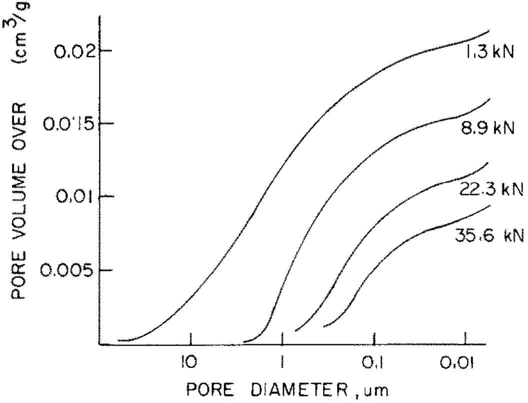

Fig. 8. Mercury intrusion porosimetry plots for dicalcium phosphate tablets compressed at different compression forces. Flat-faced tablets with 1.04 cm diameter were used.

As opposed to this, dicalcium phosphate [5] behaves conventionally. A Heckel plot, based on the true density of 2.31 g/cm^3 is shown in Fig. 7 and is quite linear (after the usual region of curvature due to rearrangement and brittle fracture). A pore distribution plot is shown in Fig. 8. It is noted, in contrast to Fig. 3, that the entire curve is affected by compression. These data, as well as surface area data are shown in Table 4. It is noted that the surface area obtained from porosimetry is about 0.8 m^2/g, so that the difference between this and the area obtained by gas adsorption (2 m^2/g) must be due either to pores below 60 Å or to deviations from the tube model. The average particle diameter of the dicalcium phosphate studied was 200 μm. It might, on the surface seem to be physically unfeasible that pores in the finer than 60 Å region could account for the discrepancy in surface area. However, the following argument will show that the smaller pores could quite easily account for the surface area difference.

At 35.6 kN compression force, the total pore volume is 0.0094 ml/g. The measured porosity (by geometry) is 0.14 cm^3/cm^3, i.e. 0.14 cm^3/2.31 g = 0.070 cm^3/g (using a true density of 2.31 g/cm^3). This means that 0.061–0.009 = 0.05 cm^3/g are not accounted for by porosimetry. The average diameter of the particles is 200 μm, i.e. there are $(1.99 \times 0.02^3 \cdot \pi/6)^{-1} = 1.2 \times 10^5$ particles/g. If the "small" pores average 30 Å in diameter, then it would take Q cm of pores to obtain an area of $(2 - 0.8) = 1.2$ m^2/g where Q is given by:

$$Q \cdot \pi \cdot 30 \times 10^{-8} = 1.2 \times 10^{4} \qquad (6)$$

i.e. $Q = 1.3 \times 10^{10}$ cm total, or $1.3 \times 10^{10}/1.2 \times 10^5 = 10^5$ cm of pores per particle. If each pore is 200 μm = 0.02 cm long then there would be $10^5/0.02 = 5 \times 10^6$ pores per particle. The "end" of each pore occupies an area of $\pi \cdot (30 \times 10^{-8})^{-2}/4 = 7 \times$

TABLE 4

COMPRESSIBILITY DATA FOR DIBASIC CALCIUM PHOSPHATE DIHYDRATE

	Compressional force (kN):									
	1.3	2.6	4.45	8.9	13.4	17.8	22.3	31.2	35.6	44.5
Geometic density (g/cm^3)		1.40	1.53	1.70	1.76	1.82	1.88	1.95	1.99	2.01
Density from porosimetry (g/cm^3)	1.49		1.67	1.87	1.93	2.11	2.04		2.14	
Pore volume (cm^3/g) (from porosimetry)	0.021	0.020		0.017	0.015		0.012		0.0094	
Surface area from porosimetry (cm^2/g)	0.70		0.72	0.83	0.73	0.80	0.96		0.86	
$\ln(1-\{\rho'/2.31\})$	−1.03		−1.29	−1.66	−1.80	−2.47	−2.15		−2.59	

10^{-16} cm^2 of the particle surface so that a total of $5 \times 10^6 \times 7 \times 10^{-16} = 3.5 \times 10^{-9}$ cm^2 of each particle surface is the area of the "entry" of the small pores. Since a 200-μm diameter particle has a geometric surface area of $\Pi \times 0.02^2 = 1.3 \times 10^{-3}$ cm^2, this can quite easily accommodate the entry surface area of the pores.

It is seen, hence, that the fine pore space in dicalcium phosphate is part of the Heckel pore space, whereas it is not part of the Heckel pore space in tricalcium phosphate.

Again it should be pointed out that the fact that the tube model is used for the pore population makes the conclusions presented here somewhat speculative. However, taking all the presented facts as a whole substantiates the presented views. A large body of literature exists using the bundle of tubes model as basic hypothesis, and hence it has been felt to be reasonable to use it here as well.

It should finally be pointed out that Heckel plots are usually carried out in pharmaceutical investigations in pressure ranges compatible with those used in conventional tableting (corresponding to the ones used in this study). It is possible that much higher pressures would eventually affect the "occluded" pore space. This would be tantamount to considering the pore space as a binary space, one part being affected by low pressure and one being affected by high pressure. In such a view the density of 1.92 g/cm^3 used here for tricalcium phosphate would be a value found by iteration for another substance.

Conclusion

It is shown that tricalcium phosphate obeys the Heckel equation only if a particle density of 1.92 g/cm^3 (rather than the true density of 3.1 g/cm^3) is used.

The pore space involved in the compression process would appear to (primarily) be the part having pore diameters between 0.5 and 2.0 μm.

As opposed to this, dicalcium phosphate dihydrate compresses in conventional fashion with all pores being reduced in volume and diameter upon compression.

Acknowledgements

We thank Ortho Pharmaceutical Company, Raritan, NJ, U.S.A. and Sandoz Pharmaceutical Company, E. Hanover, NJ, U.S.A. for support for this work.

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