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# Dicalcium phosphate dihydrate for direct compression: Characterization and intermanufacturer variability

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**Abstract**

The structure, dehydration behaviour, and particle characteristics of the two currently available commercial brands of unmilled dicalcium phosphate dihydrate (DCPD) for direct compression, Emcompress and DiTab, were studied. The two brands have very similar properties, differing significantly only in intraparticle porosity. As a consequence, their compression and flow properties are effectively identical. The characteristics of Emcompress and DiTab were compared with those of two DCPD powders, Calipharm (whose properties are typical of milled DCPD preparations) and Kyowa (whose properties are in many respects atypical). It is concluded that the processing undergone by unmilled DCPD for direct compression does not cause major changes in crystal structure, mechanical and surface properties with respect to typical powders. However, there are considerable differences in dehydration behaviour, which can probably be attributed to the larger mean particle size and different particle structure of the direct compression preparations.

*Key words:* Dicalcium phosphate dihydrate; Direct compression; Dehydration behavior; Particle size analysis; Compression properties; Intermanufacturer variability

## 1. Introduction

Dicalcium phosphate dihydrate (DCPD) is widely used as an excipient in solid dosage forms, due to its low hygroscopicity and considerable physical and chemical stability. For production of tablets by direct compression, unmilled DCPD is generally used, since it combines the above advantages with good compression and flow properties and relatively low cost (Carstensen and Ertell, 1990; Shangraw, 1991). Two commercial brands of unmilled DCPD for direct compression are currently available, Emcompress and DiTab (Toy and Walsh, 1987; Fischer, 1992).

One disadvantage of DCPD is its tendency to lose its lattice water (Rabatin et al., 1960; Dugleux

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and Sallier Dupin, 1967a; Ball and Casson, 1973). This process is strongly affected by temperature and humidity (Dugleux and Sallier Dupin, 1967b; De Haan et al., 1990). This may have serious effects on the chemical stability of some active principles or on the properties of dosage forms (Lausier et al., 1977; Vila-Jato et al., 1985; Patel et al., 1988; De Haan et al., 1990).

In a previous study (Landín et al., 1994) we compared the particle characteristics and dehydration behaviour of five powder DCPDs, each produced in a different country. Those produced in Germany, the U.K., Spain and the U.S.A. had very similar properties, while that produced in Japan differed markedly in several respects. This can presumably be attributed to differences in manufacturing processes, and should clearly be taken into consideration in the course of product selection.

In the present study, Emcompress and DiTab have been characterized in terms of properties relevant for their use as excipients in solid dosage forms. We have also compared the characteristics of the two brands with the previously reported (Landín et al., 1994) characteristics of a 'typical' powder brand (Calipharm, from the U.K.) and an 'atypical' powder brand (Kyowa, from Japan). The aim of this approach was to determine whether the processing of DCPD intended for direct compression leads to differences in pharmaceutically relevant properties with respect to milled DCPD.

## 2. Materials and methods

### 2.1. Materials

The two direct compression DCPDs studied were samples of Emcompress (Edward Mendel) and DiTab (Rhone-Poulenc). The powder samples were Calipharm (Albright and Wilson) and Kyowa (Kyowa).

### 2.2. Powder X-ray diffraction

Measurements were carried out at room temperature, on a Siemens D5000 X-ray diffractometer using monochromatic CuK$\alpha$ radiation and a scanning rate of 0.25° $2\theta$/min over the range 3–73° $2\theta$. Samples for analysis were prepared by pressing the powder into a sample holder and smoothing with a glass slide.

### 2.3. Infrared spectroscopy

Infrared spectra in the 200–4000 $cm^{-1}$ region were recorded on a Mattson Cignus 100 spectrophotometer using KBr pellets.

### 2.4. Thermogravimetric analysis

The loss of weight of the DCPD samples was determined thermogravimetrically using a Mettler TG 50 thermobalance linked to a TC 10a processor (Mettler Instruments, Griefensee, Switzerland). Powder samples weighing 40–60 mg were heated at 10°C per min from 50 to 250°C. The results were used to calculate the activation energy of each dehydration stage from the Arrhenius equation (Dugleux et al., 1965).

### 2.5. Differential scanning calorimetry

DSC thermograms of 0.5–3.0 mg DCPD samples were recorded at a heating rate of 10°C/min in a Mettler DSC 30 linked to a TC 10a processor, either in an open aluminium pan under a 100 ml/min current of nitrogen or in a hermetically sealed pan. The enthalpy of each dehydration stage was determined by integration of the thermogram peaks.

### 2.6. Immersion calorimetry

Immersion calorimetry measurements were carried out in duplicate in a Tronac model 458 Solution Calorimeter as described by Parker and Rowe (1991).

### 2.7. Scanning electron microscopy

Samples were mounted on double-sided tape on aluminium stubs, coated with gold under vacuum and examined under an ISI 60 scanning electron microscope.

### 2.8. Particle size analysis

Particle size distributions were determined in triplicate using a Coulter LS 100 Laser Scattering Particle Size Analyser. The results are expressed in terms of mean surface diameter ($d_s$).

### 2.9. Nitrogen adsorption

The specific surface area was determined in a Micromeritics ASAP 2000 apparatus. Samples were first degassed by heating in vacuo for 24 h at 60°C and a pressure of $10^{-3}$ mmHg. Nitrogen adsorption took place at 77 K and relative pressures from 0.001 to 0.98. The specific surface areas ($s_w$) were calculated from the formula:

$$s_w\ (m^2/g) = 4.37 V_m\ (cm^3/g)$$

where $V_m$ is the volume of nitrogen necessary to form a monolayer which can be calculated from the BET equation (Stanley-Wood et al., 1990).

Pore size distributions were calculated from the nitrogen adsorption isotherms by the BJH method (Stanley-Wood, 1983).

### 2.10. True density

True particle densities were determined in triplicate using a Quantacrome Model PY2 helium pycnometer.

### 2.11. Bulk density

Tapped bulk density was measured in a Hosokawa powder tester under tapping at 50 taps/min for up to 20 min. The results were used to calculate compressibility and flowability index (Thomson, 1984).

### 2.12. Compression properties

Samples were compressed in a Korsch EKO excentric press equipped with Kistler 9031A

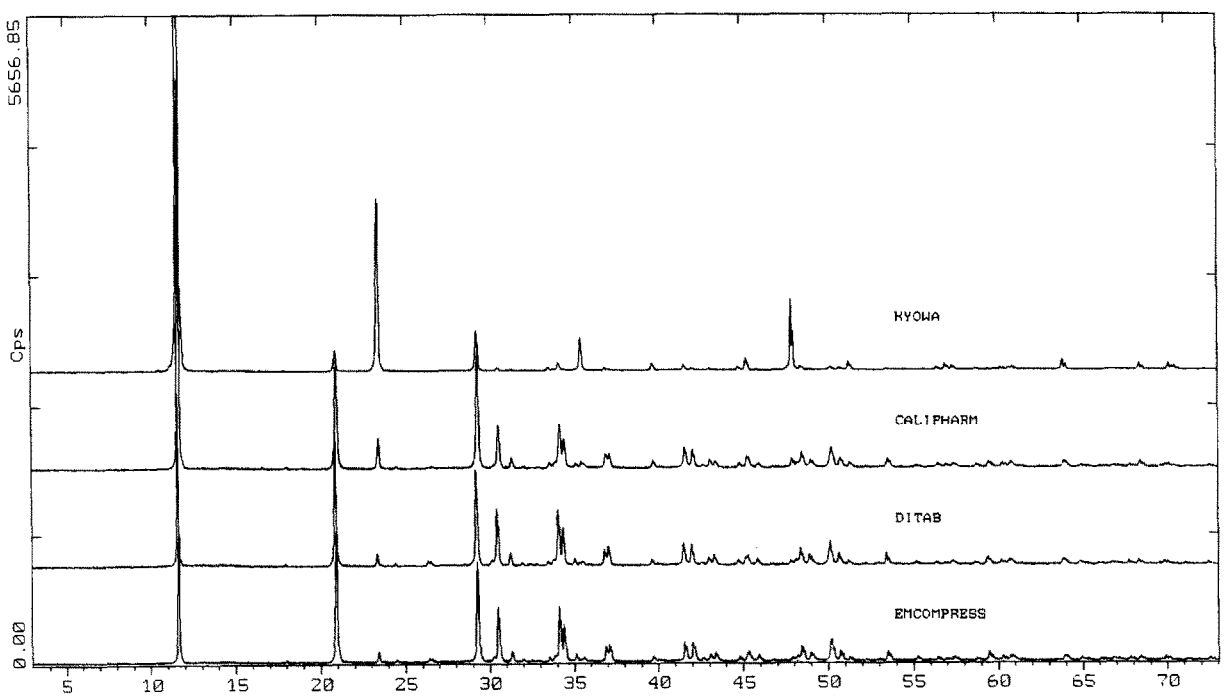


Fig. 1. X-ray diffraction scans of the DCPD samples.

piezoelectric pressure transducers and interfaced to a Hewlett Packard 85 computer via an HPIB data monitoring system (Martínez-Pacheco et al., 1985). The die wall and punch faces were lubricated with a 5% w/w suspension of magnesium stearate in acetone. Mean yield pressures under load were determined using Heckel plots of the data from compression force-displacement cycles (Humbert-Droz et al., 1982).

## 3. Results and discussion

The X-ray diffraction spectra (Fig. 1) of Emcompress, DiTab and Calipharm all display a very similar pattern, coinciding with that of synthetic brushite, JCPDS pattern 9–77 (JCPDS, 1989), while the Kyowa spectrum is markedly different and coincides with that of natural brushite, JCPDS pattern 11–293 (JCPDS, 1989).

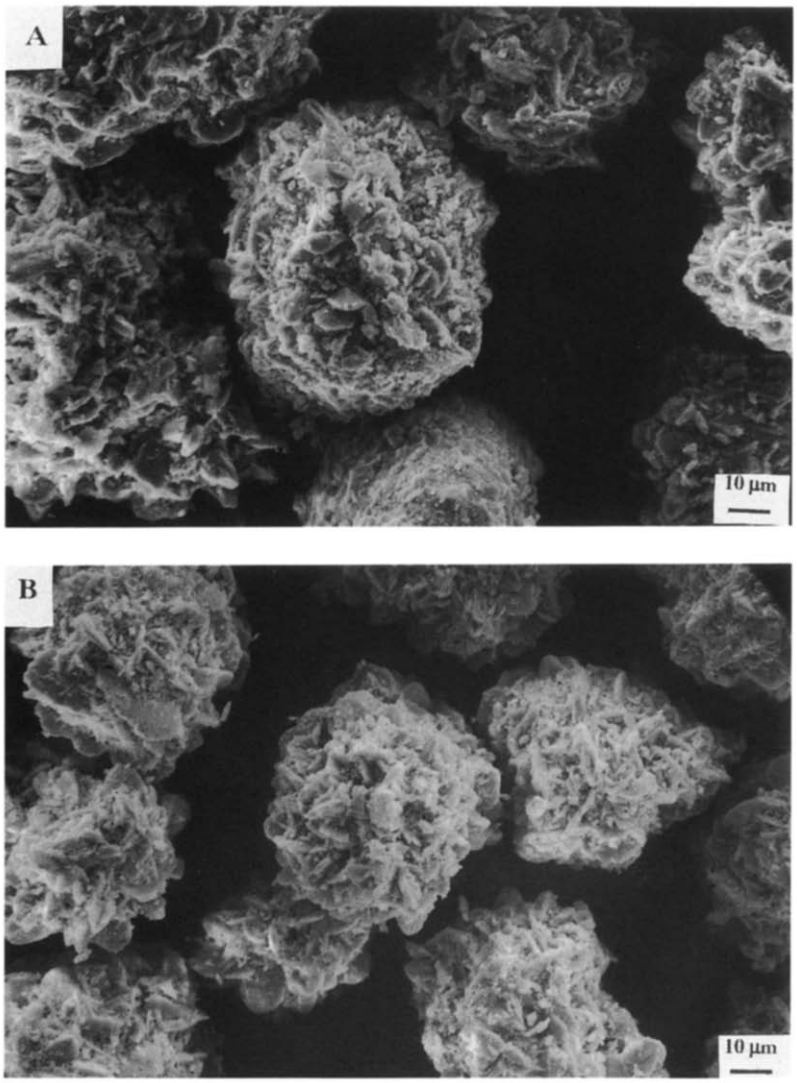


Fig. 2. Scanning electron micrographs of the unmilled DCPDs: (A) Emcompress; (B) DiTab.

Table 1
Mean particle size and specific surface on the four DCPDs studied

| Product | Mean particle size ($\mu$m) | Surface area ($m^2/g$) |
|---|---|---|
| Emcompress | 57.33 (1.19) | 0.85 (0.10) |
| DiTab | 57.22 (0.44) | 0.77 (0.08) |
| Calipharm | 5.09 (0.11) | 1.89 (0.07) |
| Kyowa | 32.93 (0.12) | 0.98 (0.08) |

Scanning electron micrographs of Emcompress and DiTab reveal particles of very similar appearance – rough surface, spherically shaped, tightly fused agglomerates – (Fig. 2) which are, however, very different from those of Calipharm and Kyowa – small irregular-shaped agglomerates and large plate crystal, respectively – (Landín et al., 1994). This, and the larger mean particle size of the direct compression products (Table 1), can probably be attributed to differences in manufacturing. The mean particle sizes of Emcompress and DiTab are almost identical (Table 1). The differences in particle size (Fig. 3) between these and the other two products are directly reflected in their specific surfaces (Table 1). The slight difference in specific surface between Emcompress and DiTab can be attributed to the greater internal porosity of Emcompress agglomerates (Fig. 4).

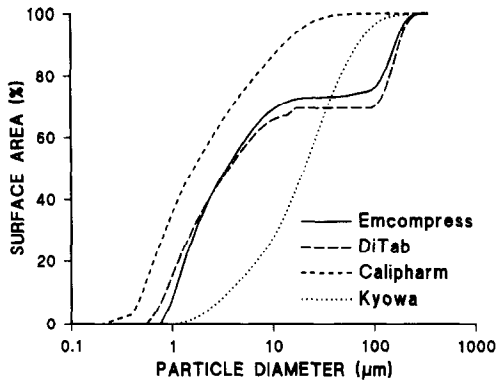


Fig. 3. Particle size distribution in the DCPD samples.

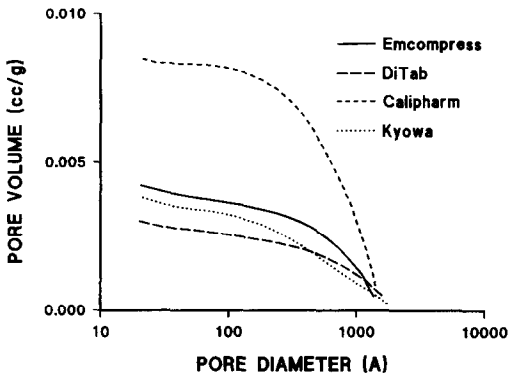


Fig. 4. Pore size distribution in the DCPD samples.

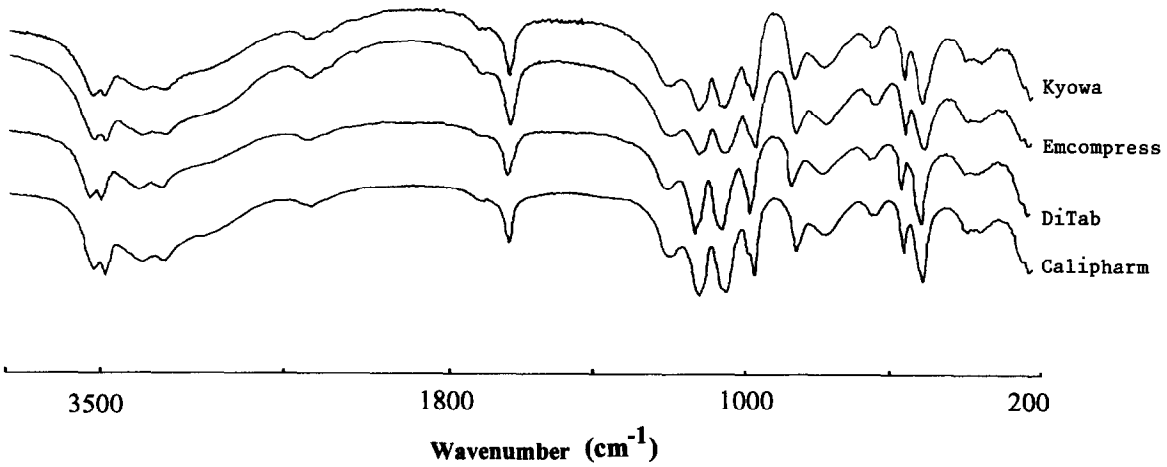


Fig. 5. IR spectra of the DCPD samples.

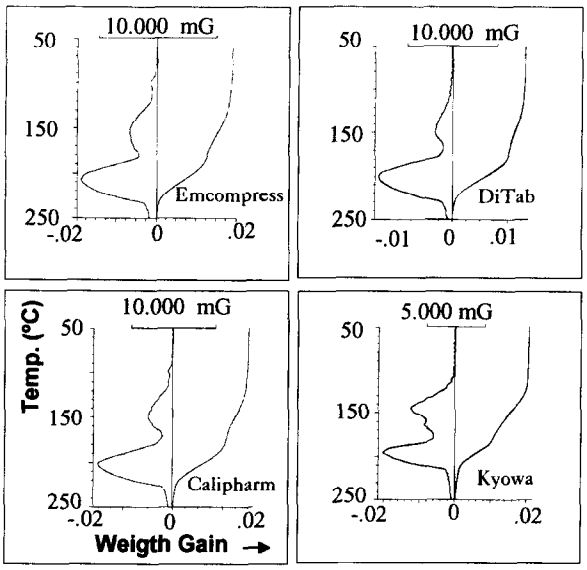


Fig. 6. TGA curves for the DCPD samples.

We have paid special attention to the form in which water is present in these products and to DCPD-water interactions at the particle surface. The IR spectra of Emcompress and DiTab show bands characteristic of lattice water (663, 3488 and 3522 $cm^{-1}$) and of weakly bound water (3158 and 3268 $cm^{-1}$) (Leconte et al., 1955; Fraissard et al., 1965); the two spectra are almost identical and very similar to those of Calipharm and Kyowa (Fig. 5). Since IR spectroscopy does not always reveal important differences in water-binding properties, we also used thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) to characterize dehydration behaviour. In TGA (Fig. 6), the characteristic weight-loss peaks of the DCPD powder products at 150°C ('step 2') and 200°C ('step 3') (Boullé and Jolibois, 1948) are also displayed by the Emcompress and DiTab (Table 2). It is interesting to note that the percentages of water lost at each step by Emcompress and DiTab are similar and tend to be intermediate between those lost by Calipharm and Kyowa (Boullé and Dupont, 1955). The activation energies associated with steps 2 and 3, on the other hand, are similar for Emcompress, DiTab and Calipharm but markedly higher for Kyowa (Table 2). This similarity between the products with synthetic brushite structure suggests that particle size may have a considerable influence on the dehydration process. The greater loss of lattice water at step 2 by Emcompress and DiTab than by Calipharm may be related to catalysis of dehydration by water vapour: this autocatalysis is probably more important in the direct compression products, in which the tightly fused aggregate (Table 1) can be expected to impede the escape of water vapour from individual crystals. The more marked differences in dehydration behaviour between the direct compression products and Kyowa, on the other hand, should be attributed not only to differences in particle size but also to the difference in crystal structure.

TGA of Emcompress and DiTab (Fig. 6) also revealed an additional peak, not present in the TGA curves of the DCPD powders, at around 100°C. Weight losses from the powders and the direct compression products up to this temperature were, however, of the same order of magnitude (Table 2). This peak may therefore reflect differences between the two types of DCPD in

Table 2
Characteristics of TGA and DCS curves of the four DCPDs studied

| Product | TGA | | | | | | | | DSC, enthalpy ($J/g^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Weight loss (% w/w) | | | | | Activation energy ($J\ mol^{-1}$) | | | Open pan | | | Sealed pan |
| | 100°C | 1st step | 2nd step | 3rd step | Total | 1st step | 2nd step | 3rd step | 1st step | 2nd step | 3rd step | 1 step |
| Emcompress | 0.40 | 0.51 | 5.94 | 14.34 | 20.79 | 283.72 | 78.39 | 148.87 | 5.25 | 97.10 | 388.60 | 481.69 |
| DiTab | 0.32 | 0.23 | 5.36 | 14.45 | 20.04 | 286.49 | 86.20 | 148.62 | 0.92 | 84.76 | 381.92 | 470.79 |
| Calipharm | 0.45 | – | 3.82 | 17.38 | 21.20 | – | 72.52 | 143.93 | – | 57.61 | 454.00 | 463.57 |
| Kyowa | 0.20 | – | 9.79 | 11.75 | 21.54 | – | 144.74 | 248.25 | – | 179.50 | 337.70 | 502.25 |

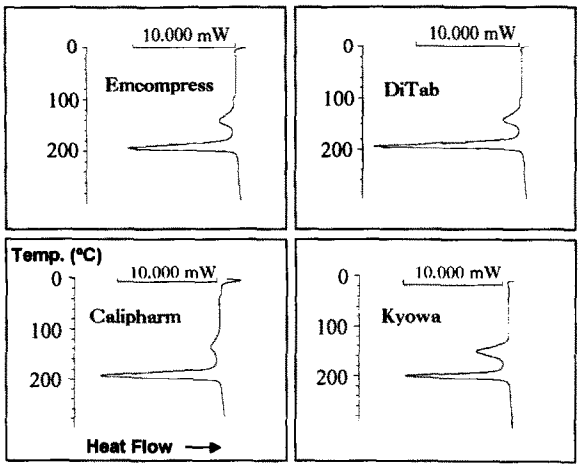


Fig. 7. DSC curves for the DCPD samples.

the particle distribution of non-lattice water, as a result of differences in manufacturing procedures. In this connection, the greater specific surface of the DCPD powders is consistent with a greater proportion of the non-lattice water being surface-adsorbed; in the direct compression products, on the other hand, non-lattice water is probably largely present in condensed form in capillary micropores. Thus, the difference between Emcompress and DiTab in the size of the additional peak may be attributable to the difference in internal porosity (Fig. 4).

Open-pan and closed-pan DSC results (Fig. 7 and Table 2) confirm the above findings, particularly as regards the autocatalysis of dehydration by water vapour.

Surface interactions with water were investigated by immersion calorimetry. In all cases, the enthalpies of immersion (Table 3) were very low. The differences between direct compression products and powders in enthalpy per unit weight can be attributed to differences in specific surface (Table 1). Thus, it can be concluded that the treatment processes used in the production of DCPD for direct compression do not affect the surface energy of the product.

Table 3
Mean enthalpies of immersion per unit mass and per unit area of the four DCPDs studied

| Product | Enthalpy of immersion | |
|---|---|---|
| | $-J\,g^{-1}$ | $-J\,m^{-2}$ |
| Emcompress | 0.26 (0.01) | 0.31 (0.02) |
| DiTab | 0.22 (0.04) | 0.28 (0.06) |
| Calipharm | 0.53 (0.13) | 0.28 (0.07) |
| Kyowa | 0.31 (0.05) | 0.32 (0.02) |

Table 4
Mean flow and densification characteristics of the four DCPDs studied (standard deviations in parentheses)

| Product | Compressibility (%) | Flowability index | Mean yield pressure (MPa) |
|---|---|---|---|
| Emcompress | 17.5 | 72 | 352.8 (5.7) |
| DiTab | 16.8 | 75 | 353.9 (6.9) |
| Calipharm | 54.8 | 39 | 348.4 (8.3) |
| Kyowa | 49.7 | 46 | 344.4 (14.9) |

In view of the value of Emcompress and DiTab as filler-binders, we compared the compression and flow properties of the direct compression and powder products. Both direct compression products display excellent flow properties, with compressibility and flowability index values being almost identical, whereas the flow properties of the DCPD powders are very poor (Table 4). This can be attributed to differences not only in mean particle size but also in particle morphology. Finally, as expected for a material which is compressed largely as a result of particle fragmentation, mean yield pressures are similar for all four products.

## 4. Conclusions

The principal conclusion of this study is that Emcompress and DiTab are very similar in structure, particle characteristics and dehydration behaviour. Emcompress has slightly higher internal porosity, but this has no appreciable effect on compression and flow properties, which are likewise very similar for the two products. Comparison of Emcompress and DiTab with two DCPD powders (Calipharm and Kyowa) shows that they are most similar to the typical powdered product Calipharm, with which they share the same crystal structure (synthetic brushite). However, there are differences in dehydration behaviour, which

may be related to differences in particle size, between the unmilled DCPDs and the typical milled product.

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