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PHYSICAL AND CHEMICAL PROPERTIES OF CALCIUM PHOSPHATES FOR SOLID STATE PHARMACEUTICAL FORMULATIONS

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Abstract:

The physical and chemical properties of pharmaceutical phosphates are reviewed, with particular emphasis on chemistry of syntehsis, nomenclature, physico-chemical properties and tableting characteristics (other than Athy-Heckel qualities, which are covered elsewhere (Carstensen et al., l989) and dissolution characteristics.

Introduction.

The calcium phosphates, notably dibasic calcium phosphate, anhydrous and dihydrate, and hydroxyapatite (often referred to as tricalcium phosphate) have gained prominence in pharmaceutical and dietary supplement formulations. The reasons for this is (a) their high calcium content, which lends to the label claim of this element, (b) the desirable flow and compressibility characteristics which can be imparted upon them by skillful manufacture, and (c) their reasonably low cost.

Much is not understood about these phosphates, and much is misunderstood about them, and it is the intent of this article to shed some light on the general behavior profile of these substances.

Nomenclature.

Dibasic Calcium Phosphate, Anhydrous, is $CaHPO_4$, and is generically referred to as *dicalcium phosphate anhydrous*, or simply dicalcium phosphate. Commercial grades of this are A-Tab™ (Stauffer, Rhone-Poulenc) and Dicaphos™ (Budenheim).

Dibasic Calcium Phosphate, Dihydrate, is $CaHPO_4,2H_2O$ and is generically referred to as *dicalcium phosphate dihydrate*. Commercial Grades of this are Di-Tab™ (Stauffer, Rhone-Poulenc) and Emcompress (Mendell).

Hydroxyapatite is $Ca_5(OH)(PO_4)_3$. This is commercially available as Tri-Tab™ (Stauffer, Rhone-Poulenc). This is frequently (but erroneously) referred to as Tricalcium Phosphate. Tricalcium phosphate ($Ca_3(PO_4)_2$) does exist (as an α and ß form) but is not commercially available on large scale for tablet work.

Syntheses.

The calcium phosphates are synthesized from phosphoric acid (H_3PO_4, frequently referred to in the following simply as its anhydrate, P_2O_5) and slaked lime ($Ca(OH)_2$). The over-all stoichiometry would be as follows:

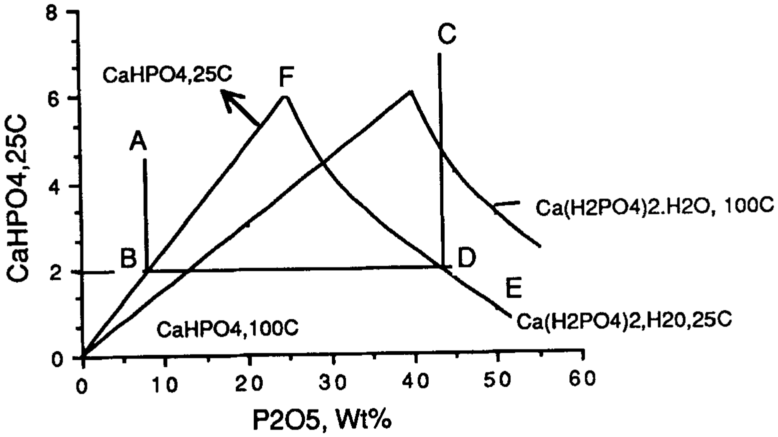

Fig. 1. The system CaO-P2O5-H20 at 25°C and 100 °C

$H_3PO_4 + Ca(OH)_2) \text{-->} CaHPO_4 + 2H_2O$ (1)

$H_3PO_4 + Ca(OH)_2) \text{-->} CaHPO_4,2H_2O$ (2)

$3\ H_3PO_4 + 5\ Ca(OH)_2 \text{-->} Ca_5(OH)(PO_4)_3 + 9\ H_2O$ (3)

The situation is, however, much more complicated than these simple, stoichiometric reactions would imply. The processes described in Remington (l985) differ from those above, but the latter refer to processes for food grade phosphates.

Fig. 1 shows the phase diagram of the system $CaHPO_4,2H_2O/CaHPO_4$. The diagram shows two phase lines, one at 25^{o}C and one at 100^{o}C. The diagram should be read as follows:

If a liquid composition were made as indicated by point A, then the amount of dicalcium phosphate anhydrous dictated by the length of chord AB would precipitate, leaving a liquid of the composition denoted by the coordinates of B, i.e. 6% P_2O_5 and 2% CaO. It should be noted that the diagram is an *equilibrium* diagram and that equilibria of this type are slow in being established, and if an attempt were made to duplicate this in the laboratory in a short period of time, there would be no guarantee that the solid phase would be (all) dicalcium phosphate anhydrous.

Similarly if a (hypothetical, supersaturated) solution of composition C were allowed to sit until equilibrium were established, then an amount corresponding to CD of monocalcium phosphate ($Ca(HPO_4)_2$) would have precipitated out leaving a liquid of composition 45% P_2O_5 and 2% CaO.

Two facts are noted from the diagram: (a) that the area under the curve OADE corresponds to solutions and the area above to supersaturated systems, and (b) that dicalcium phosphate dihydrate is less soluble as the temperature increases, whereas dicalcium phosphate anhydrous has a normal temperature solubility curve.

The calcium phosphates are insoluble (by USP definition) in water. Yet there are differences between the various species. The best way of expressing solubility of an ionic compound is, of course, the solubility product, K_{so}, which for the dicalcium phosphates is defined as (Marshall, 1970):

$$K_{so} = [Ca^+][HPO_4^-]\cdot\gamma_\pm^2 \qquad (4)$$

and for hydroxyapatite is defined as (McDowel, H. et al., 1977)

$$[Ca^+]^5[OH^-][PO_4^{---}]^3\cdot\gamma_+^5\cdot\gamma_-\cdot\gamma_{PO4} \qquad (5)$$

General physico-chemical characteristics are shown in Table I.

It will be commented on at a later point that the species are kinetically dictated, and calcium phosphates of the same composition but differently produced may have different apparent parameter values.

If the diagram in Fig. 1 is expanded to higher calcium contents, then a phase diagram as shown in Fig. 2 results. The area marked OFE is

Table I. Physico-chemical Profiles of the Phosphates

	Dicalcium Phosphate[a]	Hydroxyapatite[b]
pH (20% Slurry)	7.0-7.4	6.6-7.0
K_{so} - 25°C	2.5×10^{-7}	4.7×10^{-59}
K_{so} - 37°C	1.9×10^{-7}	2.3×10^{-59}
Solubilty in Acid	Yes	Yes

[a] Unmilled dicalcium phosphate dihydrate (Ditab™)

[b] Tritab™

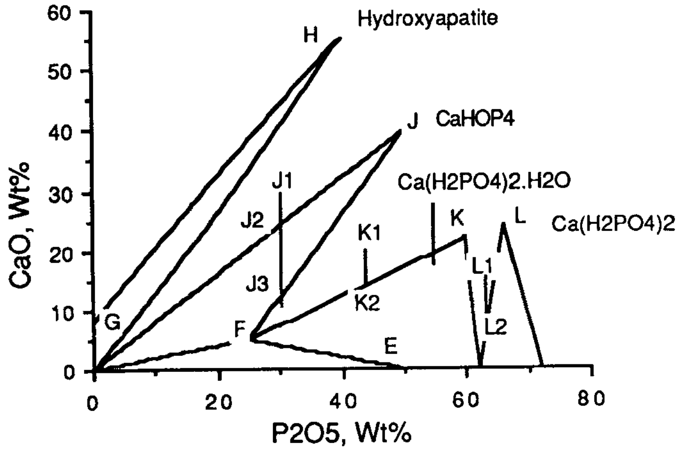

Fig. 2 CaO-H2O-P2O5 System

the same as that in Fig. 1. Solutions within the triangles are supersaturated in the salt denoted by the apex, e.g. in triangle GHO, hydroxyapatite will precipitate out, until the lower chord line is reached and the solution dictated by the point on the chord will the liquid composition in equilibrium with the solid phase indicated (Hydroxyapatite for chord OH for instance). In the white areas, inbetween triangular areas, there will be a precipitation of a mixture of the two bordering salt compositions, e.g. a (supersaturated) composition at J1 will precipitate hydroxyapatatite until J2 and then anhydrous calcium phosphate until J4 and, hence, a mixture of anhydrous dicalcium phosphate and hydroxyapatatite will be in equilibrium with a liquid of the composition J4. A (supersatureated) composition of J3 will simply precipitate anhydrous dicalcium phosphate until J4 has been reached. Similarly monocalcium phosphate hydrate may be precipitated from compositions in the triangle FKE and anhydrous monocalcium phosphate may be precipitated from compositions in the triangle ELM. Mixtures of monocalcium phosphate and monocalcium phosphate dihydrate may be precipitated in the area EKL inbetween triangles and mixtures of dicalcium phosphate and monocalcium phosphate dihydrate may be precipitated in the area JFK inbetween triangles.

All these observations are *equilibrium* considerations (VanWazer, l958) and it is noted, for instance, that dicalcium phosphate dihydrate is nowhere to be seen in the diagram. In fact, this is a metastable species the production of which is *kinetically controlled,* It is therefore not surprising that the physical properties of this compound is producer dependent. For example, if seeding is carried out, this, in a kinetically dictated situation, may promote the growth of a species which is not the type indicated in an equilibrium diagram.

Although not much is known about the actual manufacturing conditions of the various species, it is known that anhydrous dicalcium phosphate can be by direct precipitation (see Fig. 1) or made by first precipitating the dihydrate, and then dehydrating this product thermally. Although chemically and crystallographically identical, e.g. in their X-ray patterns, the materials made by these two different processes can differ markedly in physical properties such as densities, surface areas and tableting characteristics.

Compression Characteristics.

There are several aspects of importance in the compression characteristics. First of all the compression profile is (the most) important, i.e. what is the failure strength of a tablet compressed at a certain pressure. Second: the behavior vis-a-vis magnesium stearate. If the compression profile drops in relation to (a) magnesium stearate content and (b) length of mixing with magnesium stearate. In the (virtual) absense of these effects the bonding effect is (primarily) brittle fracture, in the opposite case it is plastic deformation (Carstensen, l981, Kha).

Anhydrous Dibasic Calcium Phosphate .

The compression profile of this compound is shown in Fig. 3. It should be noted (not shown) that neither amount of magnesium stearate nor intensity of mixing affects the compression profile (much).

Dicalcium Phosphate Dihydrate.

The compression profile of this compound is shown in Fig. 3 Again, there is no effect of magnesium stearate on the profile.

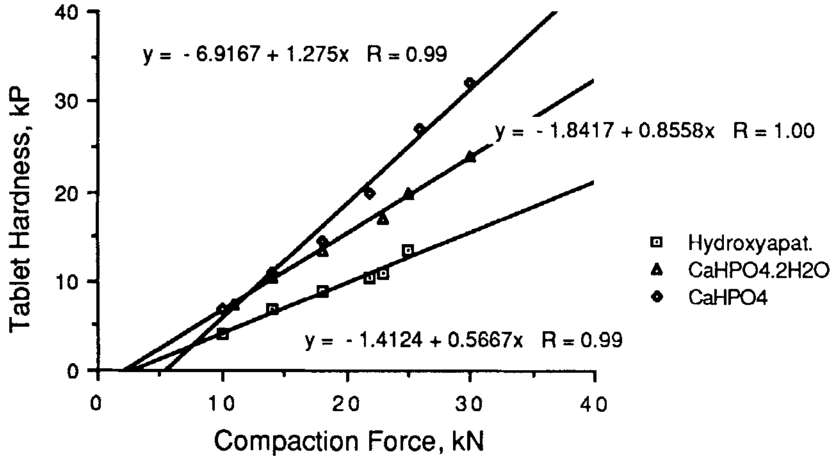

Fig. 3. Compression Profiles of A-Tab™, Di-Tab™ and Tri-Tab™

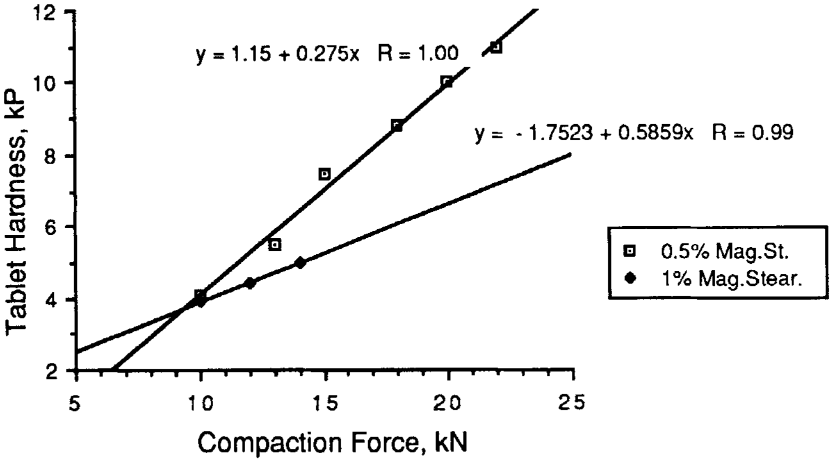

Fig. 4. Compressibility Profile for Hydroxyapatate (Tri-Tab)

Hydroxyapatite.

The compression profile of this compound is shown in Fig. 4. It is noted that there is a profound effect of magnesium stearate. At 2%, for instance, (and this is higher than usually warranted), tablets could not be made at all. Magnesium stearate effects have been reported for other direct compression ingredients as well, e.g. microcrystalline cellulose.

At pressures slightly higher than shown, it is noted that there is a slight curvature in the compression plot, indicating the approach of a critical capping pressure, beyond which the product will start to cap (Carstensen et al., l985).

Hygroscopicity.

The three calcium phosphates are relatively nonl-hygroscopic. Their moisture isotherms are shown in Fig. 5. It is noted that there is no step like curve for dicalcium phosphate dihydrate. This is presumably due to the metastable nature of this compound.

Thermal Behavior.

The thermal behavior of the calcium phosphates are such that the former shows no pattern until at very high temperature (where dehydration to higher polymers takes place for both species). For the dihydrate there are three distinct events (Fig. 6). The first, between 85 and 100°C is presumably loss of surface moisture, although the amount (judging from the area under the peak) would imply at least 10 layers of moisture. The second loss corresponds to a loss of 1/2 mole of water, and the third peak to the remaining 1.5 moles of water.

There are distinct differences between DSC's of dicalcium phosphate dihydrate in closed and open pans. These types of thermograms demonstrates the fact that moisture catalyzes the dehydration of dicalcium phosphate dihydrate (Toy and Walsh, l987), a point which, on the surface, might seem selfcontradicting.

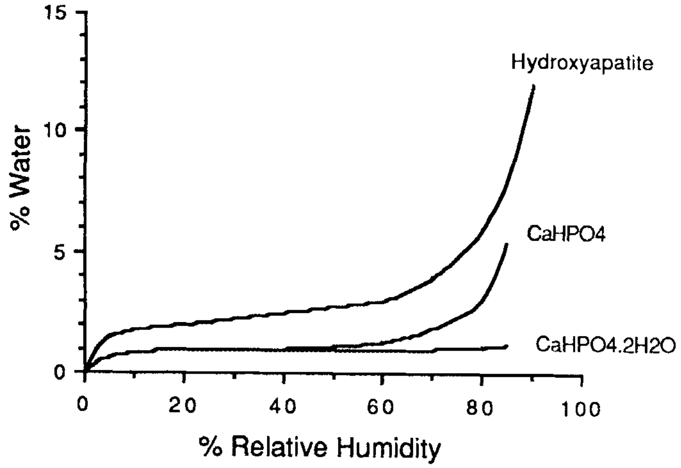

Fig. 5. Moisture Isotherms of A-Tab™, Tri-Tab™ and Di-Tab™

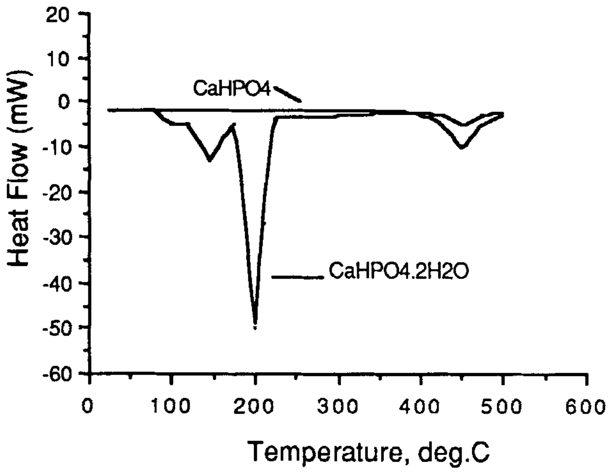

Fig. 6 DSC curves of A-Tab™ and Di-Tab™

Compatibilities and Stability.

The most advantageous use for the calcium phosphates is in vitamin-mineral supplementation. The high calcium and phosphorous contents, in combination with their good flow properties and compressional characteristics, make direct compression of vitamin-mineral tablets possible.

Table II - Properties of Calcium Phosphates

Salt	Formula	Molecular Weight	% Ca Theory	%Ca Actual*	Equivalent Weight
Dicalcium Phosphate					
Anhydrous	$CaHPO_4$	136	29.5		68
Dihydrate	$CaHPO_4.2H_2O$	172	23.29	23.5	86
Hydroxy-apatite	$Ca_5(OH)(PO_4)_3$	502	39.89	38	50

There are certain incompatibilities that have been noted. Hydroxyapatite appears to be incompatible with tocopherol acetate (but not with tocopherol succinate) at higher temperatures. The reason is attributed to the large number of hydroxyl groups on the hydroxyapatite surface, and the large surface area of this excipient. Hydroxyapatite is also prone to isomorphic ion substitution, barium, strontium, iron and magnesium, for instance may substitute for calcium in the lattice, fluoride and chloride in the hydroxy positions and carbonate in the phosphate positions. Yet the marketed grades are quite uniform.

The calcium salts themselves are quite unaltered by storage, except dicalcium phosphate has a tendency of giving off moisture abore 40-45°C. This can give rise to some *apparent* incompatibilities at higher temperatures, where the released moisture may interact with drugs, vitamins and other escipients. To extrapolate such findings to room

Table III Physical Properties of Calcium Phosphates.

	Dicalcium Phosphate Anhydrous	Dihydrate	Hydroxy-apatite
Surface Area (m^2/g)	30	2	77
Density (g/cm^3)			
True	2.89	2.31	3.15
Bulk (Tapped)	0.76	0.94	0.96
Bulk (Loose)	0.70	0.83	0.88
Crystal System*	Triclinic	Monoclinic	Triclinic

*From A.D.F.Toy (1973)

temperature would be erroneous, since dicalcium phosphate dihydrate does not dehydrate at this temperature.

The salts also suffer from having a high true density. During dissolution testing, this will make the disintegrated part of the dosage form settle in a cone at the bottom of the dissolution apparatus, and this can give rise to a faultily slow dissolution.

Physico-Chemical Properties.

Molecular weights, calcium contents, formulae and equivalent weights are shown in Table II.

Other physical properties of interest are shown in Table III.

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