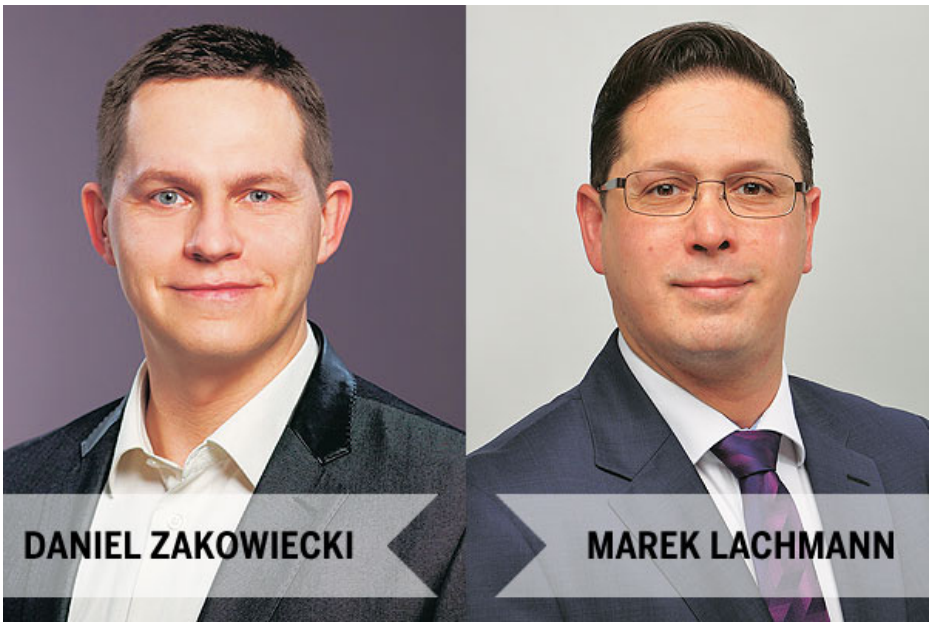
Beyond just a filler – application of calcium phosphates in direct compression formulations

By EP News Bureau on December 5, 2017



***Daniel Zakowiecki, Marek Lachmann** and **Tobias Heß Chemische Fabrik Budenheim**, in this article outlines the most important properties of various grades of calcium salts of orthophosphoric acid*

Calcium phosphates have been used in the pharmaceutical technology for many years. They have many physical and chemical properties that make them ideal candidates for the production of solid oral dosage forms. They are mainly used as fillers in order to bulk up formulations [1] however, the function of calcium phosphates goes far beyond mere filler and the adequate utilisation of their full functionality can support achieving the intended formulation goals.

Calcium phosphates are inorganic substances of mineral origin and therefore are characterised by exceptional chemical stability. For the same reason, they are compatible with most of known drug substances. The few exceptions include indomethacin and tetracycline antibiotics which form with the calcium ions hardly absorbable complexes. Tribasic calcium phosphate (USP) shows incompatibility with the tocopheryl acetate which is related to the large number of hydroxyl groups on the surface of the substance. [1,2]

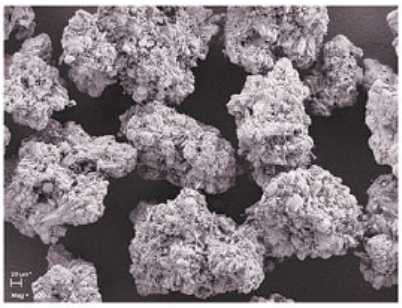


Fig. 1 | SEM picture of DI-CAFOS® D160

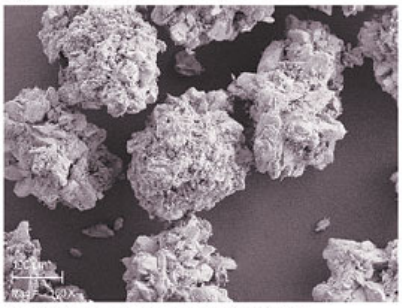


Fig. 2 | SEM picture of DI-CAFOS® A150

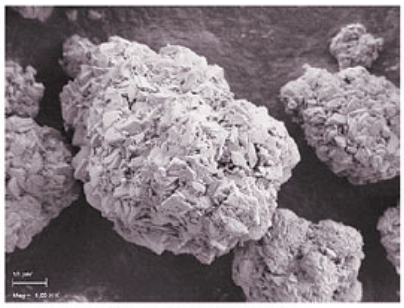


Fig. 3 | SEM picture of DI-CAFOS® A60

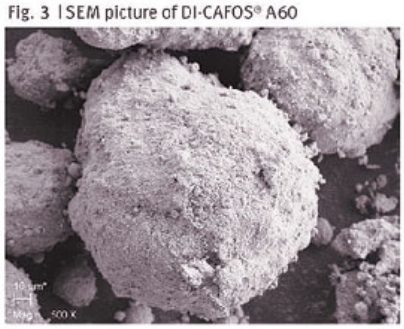


Fig. 4 | SEM picture of TRI-CAFOS® 500

Calcium salts of orthophosphoric acid do not interact with water and therefore can be successfully used in any technological operations involving water as a completely inert densifier. Due to the very high content of calcium and phosphorus they are very often used in dietary supplements. Especially hydroxyapatite finds wide spread use due to its calcium to phosphorous ratio which is identical to the one present in human bones.

Calcium phosphate based excipients possess many functional properties making them ideal candidates for direct compression process. Due to their favourable particle size and shape calcium phosphates exhibit excellent flowability. Furthermore, they enable to govern the flow pattern of poorly flowable powders, which allows for relatively easy preparation of tableting mixtures without the granulation. Very high density of calcium salts of orthophosphoric acid allows either using of larger amounts of excipients without increasing the size of the dosage form or decreasing it when the same quantity of excipient is used.

Dibasic calcium phosphates are hard, inorganic compounds which during compression undergo mainly brittle fracture. Because of that property they show very good compaction properties allowing preparation of hard tablets. In addition to that tablets made with calcium phosphates do not expand in volume upon ejection from the die. A phenomenon commonly observed after decompression of elastic or plastic-elastic materials. Another essential feature of calcium phosphates is their low lubricant sensitivity. Increased amounts of lubricants or longer mixing time do not significantly affect the compaction properties of powder mixtures containing calcium phosphates.

There are many different types of calcium phosphates available in the pharma market including coarse DC grades as well as fine materials for granulation processes. This article outlines the most important properties of various DC grades of calcium salts of orthophosphoric acid:

- dibasic calcium phosphate anhydrous: DI-CAFOS® A150 and DI-CAFOS® A60
- dibasic calcium phosphate dihydrate: DI-CAFOS® D160
- tribasic calcium phosphate: TRI-CAFOS 500 manufactured by the German company Chemische Fabrik Budenheim (called further Budenheim) and intended for direct compression processes. Furthermore, it presents the properties of tablets obtained from these products showing how many different formulation purposes they help to achieve.

Functional properties of calcium phosphates

Grains of dibasic calcium phosphate (DI-CAFOS® A150, DI-CAFOS® A60 and DI-CAFOS® D160) are aggregates of fine primary particles of various shapes and sizes. The SEM pictures show the almost spherical shape of the calcium phosphate particles (Fig 1 – 3). At the same time the surface is uneven and well-developed which facilitates uniform blending with other ingredients.

The surface of tribasic calcium phosphate (TRI-CAFOS® 500) is vast and its structure resembles a sponge (Fig. 4). Owing to this very special structure during mixing fine particles of other substances,

including API, can easily adhere to the larger particles of phosphates and improve the efficiency of mixing processes.
Calcium phosphates are characterised by very high volumetric mass density which, in conjunction with the favourable shape of the particles, provides excellent flow properties. On top of that, the elevated density allows a significant reduction of tablet or capsule size without changing their weight. Alternatively it allows using larger quantities of the substance without increasing the size of the dosage form. This is of significant importance when working with drug substances characterised by poor flowability or/and compactibility and allows overcoming these challenges.

A very important aspect is the behaviour of calcium phosphates in aqueous environment since it can impact on drug efficacy. Generally, these substances are insoluble in aqueous media at neutral or alkaline pH. However they are soluble in diluted acids, e.g. 0.1 M hydrochloric acid. That means that in acidic environment prevailing in the stomach they dissolve completely without causing the danger of retaining the drug in the tablet matrix. Consequently there is no perturbation in dissolution behaviour and absorption from the gastrointestinal tract. Furthermore, in contact with water or aqueous solutions calcium phosphates do not swell or form hydrogels. They do not disintegrate easily themselves, however, the application of small amounts of commonly used disintegrants (eg. croscarmellose sodium or cross-linked polyvinylpyrrolidone) allows producing tablets with a very short disintegration time (Fig.6).

Dibasic calcium phosphates are not hygroscopic and under conditions normally prevailing in laboratory or manufacturing area are chemically and physically stable. [1,4] Tablets containing these substances do not tend to undergo changes in tablet hardness if properly stored. [6]

The tendency of the anhydrous organic excipients to form hydrates in contact even with small amounts of water vapour being present in the air is well known. Such negative effect is not observed in the case of calcium phosphates. It should also be mentioned that the anhydrous dibasic calcium phosphate (DI-CAFOS® A60 and DI-CAFOS® A150) does not form hydrates even if mixed with water for a long time.

Tableting properties of calcium phosphate DC excipients

Dibasic calcium phosphates undergo fragmentation by brittle fracture. Due to this deformation mechanism the specific surface area of the particles is increased and thus the amount of potential binding sites between powder particles is elevated. Enhanced bonding capacity allows production of tablets of high hardness even at relatively low compression forces. [3,4] Tribasic calcium phosphate (TRI-CAFOS® 500) behaves differently and during compression undergoes mainly plastic deformations. Its high binding capacity results from the extensive specific surface area and consequently a large number of potential binding sites. [3,5]

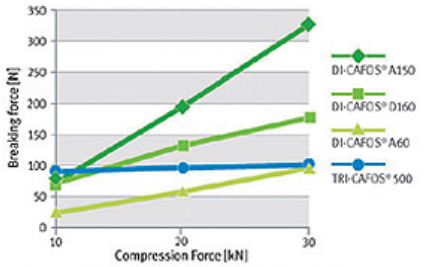


Fig. 5 | Calcium phosphate tablet hardness (breaking force)

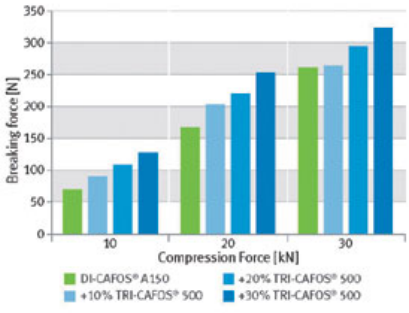


Fig. 8 | Effect of TRI-CAFOS® 500 admixture on tablet hardness

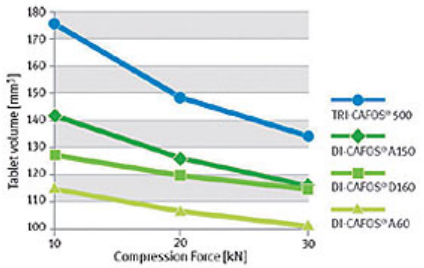


Fig. 6 | Comparison of size (volume) of the calcium phosphate tablets having the same mass

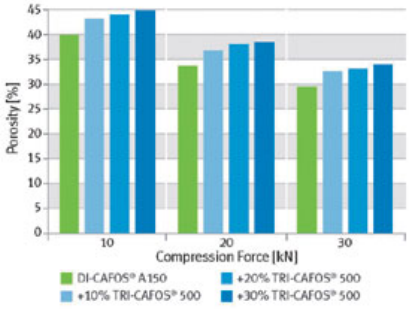


Fig. 9 | Effect of TRI-CAFOS® 500 admixture on tablet porosity

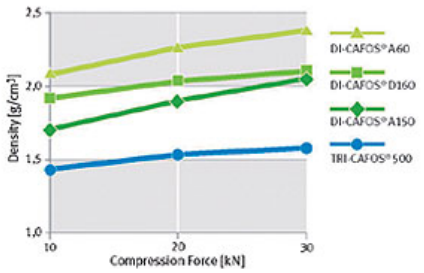


Fig. 7 | Comparison of density of the tablets containing calcium phosphates

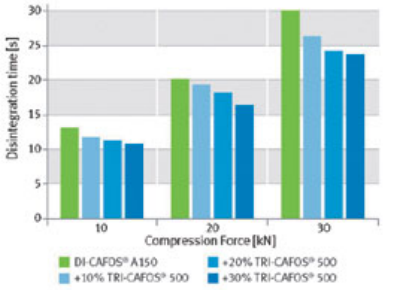


Fig 10 | Impact of TRI-CAFOS® 500 admixture on tablet disintegration time

Fig 5 – 7 show a comparison of some physical properties of the tablets obtained using four DC calcium phosphates which are manufactured by Budenheim – tablet hardness (breaking force), porosity and size expressed as tablet volume. The tablets contained 99.5 per cent of the selected calcium phosphate and 0.5 per cent lubricant (magnesium stearate). Powder mixtures were compressed into tablets using the Fette 102i rotary tablet press (Fette Compacting , Schwarzenbek, Germany) at three compaction forces: 10 kN, 20 kN and 30 kN. The results shown in Fig 5 indicate that both dibasic calcium phosphate anhydrous (DI-CAFOS® A150) and dihydrate (DI-CAFOS®

hardness (breaking force) can be obtained. It should be also noted that in the case of DI-CAFOS® A150 the compaction force has a very significant impact on tablet hardness.

DI-CAFOS® A60 is a material of exceptionally high density and very low porosity. These properties can be employed to obtain tablets or capsules of reduced size (Fig 6). Dosage forms of smaller size increase the comfort of intake and thereby enhance patient compliance, especially for pediatric or geriatric applications. Moreover, DI-CAFOS® A60 can be used to design dosage forms with high density, greater than a density of gastric fluid, which settle in the lower part of the antrum and thus affect gastric retention time. On the other hand, it should be kept in mind that the low specific surface area of DICAFOS® A60 necessitates higher compaction forces to be employed to yield tablets of sufficient hardness.

TRI-CAFOS® 500 is mostly not used as the sole filler in DC mixtures but can be successfully used as additive to commonly used filler materials. When used in tablet formulations in a concentration of 10 – 30 per cent its large specific surface area increases the bonding capacity of the powder mixtures and facilitates an increase of tablet hardness and porosity at the same time (Fig. 8 – 9). Apart from calcium phosphates (DI-CAFOS® A150 and TRI-CAFOS® 500) the tablets contained 2 per cent of croscarmellose sodium as a disintegrant and 0.5 per cent of a lubricant (magnesium stearate). It should also be noted that apart from increasing the tablet hardness, admixture of TRI-CAFOS® 500 can increase tablet matrix porosity and consequently significantly shorten disintegration time (Fig 10).

Summary

Many properties of calcium phosphates such as excellent flowability or high compactibility make them ideal candidates for direct compression processes. Since the main deformation mechanism that occurs during compression of calcium phosphates is brittle fracture, these materials are less sensitive to differences in production equipment, speed of tableting or lubricant addition. Such robustness can prove to be helpful during scaling-up of technological processes. Although this article focuses on the functional properties of phosphate for direct compression it should not be forgotten that the coarse grades of calcium phosphates can also be successfully applied in the processes of wet or dry granulation. The advantage of using them is ease of handling. In addition to high bulk density, they contain a smaller fraction of fine particles. Therefore dust generated during weighing and sieving is minimal. Until recently, the excipients were considered solely as inactive ingredients used only in order to bulk-up powders and facilitate their further processing. Nowadays however it is well known that they may also have a crucial impact on a long-term stability of drugs as well as their efficacy.

References

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