This edition of Eye on Excipients describes the benefits of using calcium phosphate excipients in direct-compression (DC) tableting applications and compares several DC calcium phosphate types.

The pharmaceutical industry has been using calcium salts of orthophosphoric acid (calcium phosphates) for many years. Calcium phosphates possess many physical and chemical properties that make them ideal candidates for use as excipients in solid oral dosage formulations. Until recently, they were considered inactive ingredients used only as fillers/diluents to bulk up formulations and facilitate their further processing [1]. Their functionality goes far beyond being a mere filler, however, and when used appropriately, they can help improve drug product efficacy as well as long-term stability.

Calcium phosphates are inorganic substances of mineral origin and are, therefore, characterized by exceptional chemical stability. For the same reason, they are compatible with most known drug substances. A few exceptions include indomethacin and tetracycline antibiotics, which combine with the calcium ions to form poorly soluble complexes. Also, tribasic calcium phosphate (USP monograph) is incompatible with tocopheryl acetate due to the large number of hydroxyl groups on the surface of the substance [1, 2].

Because calcium phosphates do not interact with water, they can be successfully used as a completely inert densifier in any process involving water. Due to their very high calcium and phosphorus content, they are often used in dietary supplements. Calcium phosphate hydroxyapatite in particular finds widespread use in supplements because its calcium-to-phosphorus ratio is identical to that of human bone [3, 4].

The functional properties of calcium-phosphate-based excipients

Figure 1
SEM images of calcium phosphate excipients

a. Dibasic calcium phosphate dihydrate (Di-Cafos D160)
b. Dibasic calcium phosphate anhydrous (Di-Cafos A150)
c. Dibasic calcium phosphate anhydrous (Di-Cafos A60)
d. Tribasic calcium phosphate (Tri-Cafos 500)
make them ideal candidates for use in DC tableting processes. They exhibit excellent flowability due to their favorable particle size and shape. Furthermore, they can improve the flow pattern of poorly flowing powders, which makes it relatively easy for formulators to prepare tableting mixtures that do not require granulation.

Many different types of calcium phosphates are available on the pharmaceutical market, including coarse DC grades as well as fine grades mainly used in granulation processes. This article outlines the most important characteristics of several DC grades of calcium phosphate, identifies their tableting properties, and discusses the different formulation challenges they can help overcome. The investigated products are dibasic calcium phosphate dihydrate, two types of dibasic calcium phosphate anhydrous, and tribasic calcium phosphate.

Functional properties of calcium phosphates

Grains of dibasic calcium phosphate excipients consist of aggregates of fine primary particles of various shapes and sizes, as shown in the scanning electron microscope (SEM) images in Figure 1a, b, and c. While the grains are almost spherical, the surface is uneven and well developed, which facilitates uniform blending with other ingredients.

Tribasic calcium phosphate particles, as shown in Figure 1d, have a large specific surface area, and their structure resembles a sponge. This allows fine particles of other ingredients, including APIs, to easily adhere to the larger calcium phosphate particles during blending and improves mixing efficiency.

Calcium phosphates are characterized by very high volumetric mass density which, in conjunction with their favorable particle shape, provides excellent flow properties. Their high density allows formulators to increase the amount of excipient in a dosage form without increasing its size or to decrease the size of a dosage form while using...
the same quantity of excipient. This is of significant importance when working with drug substances characterized by poor flowability and/or compactivity.

The behavior of calcium phosphate excipients in aqueous environments is very important, because of its potential impact on a drug product’s efficacy. Generally, calcium phosphates are insoluble in aqueous media at neutral or alkaline pH but are soluble in diluted acids, such as 0.1 mol/L hydrochloric acid. That is why they dissolve completely in the acidic environment prevailing in the stomach without any risk of retaining the drug in the tablet matrix. Consequently, there is no perturbation in dissolution behavior and absorption from the gastrointestinal tract.

Also, calcium phosphates do not swell or form hydrogels when they come into contact with water or aqueous solutions. They do not disintegrate easily themselves, but by applying small amounts of commonly used disintegrants, such as croscarmellose sodium or cross-linked polyvinylpyrrolidone, formulations can produce tablets with a very short disintegration time.

Dibasic calcium phosphates are not hygroscopic and, under the conditions normally prevailing in a laboratory or manufacturing area, are chemically and physically stable [1, 6]. Tablets containing these substances do not tend to undergo changes in tablet hardness if properly stored [8].

Anhydrous organic excipients tend to form hydrates when in contact with even small amounts of water vapor in the air, but this negative effect does not occur with calcium phosphates. Anhydrous dibasic calcium phosphate does not form hydrates even if mixed with water for an extended period of time.

**Tableting properties of DC calcium phosphate excipients**

Dibasic calcium phosphates are hard, inorganic compounds that primarily undergo brittle fracture during compression. As a result, they exhibit very good compaction properties and result in hard tablets even at relatively low compression forces [5, 6]. Tribasic calcium phosphate behaves differently, primarily undergoing plastic deformation during compression. Its high binding capacity results from the extensive specific surface area and the resulting large number of potential binding sites between particles [5, 7].

**Tables made with calcium phosphates do not expand in volume upon ejection from the die in a tablet press, which is a common phenomenon with more elastic or plastic-elastic materials.**

Tables made with calcium phosphates do not expand in volume upon ejection from the die in a tablet press, which is a common phenomenon with more elastic or plastic-elastic materials. Another essential feature of calcium phosphates is their low sensitivity to lubricants. Increased lubricant amounts or longer mixing times do not significantly affect the compaction properties of powder mixtures containing calcium phosphates.

Figures 2, 3, and 4 compare the tablet hardness (breaking force), porosity, and size (expressed as tablet volume) of placebo tablets produced using four DC calcium phosphate products manufactured by Budenheim (Di-Cafos D160, Di-Cafos A150, Di-Cafos A60, and Tri-Cafos 500). The tablets contained 99.5 percent of the selected calcium phosphate and 0.5 percent lubricant (magnesium stearate). Powder mixtures were compressed into tablets using a Fette 102i rotary tablet press at compaction forces of 10, 20, and 30 kN.

As the results show, both anhydrous and dihydrate calcium phosphates have very good tableting properties and can produce hard tablets even at relatively low compaction forces. It should be noted that, in the case of Di-Cafos A150, the compaction force has a very significant impact on tablet hardness.

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![Figure 5](image-url)

**Figure 5**

Effect of tribasic calcium phosphate (Tri-Cafos 500) admixture on tablet hardness

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![Diagram](image-url)
Di-Cafos A60 has an exceptionally high density and very low porosity, properties that can be used to produce smaller tablets or capsules, as shown in Figure 4. Smaller dosage forms can increase comfort during swallowing and enhance patient compliance, especially for pediatric or geriatric applications. Di-Cafos A60 can also be used to design dosage forms with a density greater than that of gastric fluid that will settle in the lower part of the antrum, influencing gastric retention time. On the other hand, the low specific surface area of Di-Cafos A60 necessitates higher compaction forces to ensure sufficient tablet hardness.

Tri-Cafos 500 is typically not used as the main filler in DC formulations but can be successfully used as an additive to common filler materials (co-diluent). When used in tablet formulations at concentrations of 10 to 30 percent, its large specific surface area increases the mixture’s bonding capacity and facilitates an increase in both tablet hardness and porosity, as shown in Figures 5 and 6. Apart from calcium phosphate, the tablets contained 2 percent croscarmellose sodium as a disintegrant and 0.5 percent lubricant (magnesium stearate). Note that, in addition to increasing the tablet hardness, admixture of Tri-Cafos 500 can increase tablet matrix porosity and, consequently, significantly reduce disintegration time, as shown in Figure 7.

Summary

Calcium phosphates’ excellent flowability and high compactibility make them ideal candidates for DC tableting processes. Since the main deformation mechanism that occurs during compression is brittle fracture, these materials are less sensitive to differences in production equipment, tableting speed, or lubricant addition. Such robustness can prove to be helpful during process scale-up.

Although this article focused on the functional properties of calcium phosphates for DC tableting, coarse calcium phosphate grades can also be successfully applied in wet- or dry-granulation processes, providing the advantage of ease of handling. Finally, in addition to high bulk density, calcium phosphates contain a smaller fraction of fine particles, which minimizes dust generated during weighing and sieving.

References


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