eye on excipients

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This edition of the column describes functionalized calcium carbonate, a structured mineral that serves as a multifunctional excipient. It summarizes three studies of the substance that demonstrate applications in formulation of tablets, orally disintegrating tablets, and orally disintegrating granules.

New active pharmaceutical ingredients (APIs) are increasingly challenging to formulate using excipients that comply with the regulatory requirements. It can also be difficult to find multifunctional excipients that do not multiply an already extensive regulatory burden. But functionalized calcium carbonate (FCC) is different. It's a structured mineral comprising calcium carbonate and hydroxyapatite, both of which are monographed minerals [1].

Properties

FCC is manufactured from calcium carbonate, which undergoes a process of surface re-crystallization to create a structured mineral with multiple functionalities (Figure 1). The excipient's external lamellar structure encloses a core of interconnected pores, giving the particles several desirable properties, including the ability to be used in dry granulations and to accommodate high API loading. Moreover, the surface re-crystallization process can be controlled to obtain the desired specific surface area (SSA) over a range of 40 to 120 square meters per gram (m^2/g); a particle size distribution (PSD) with a mean diameter of 2.5 to 30 microns; and pore sizes of 60 to 80 percent (v/v).

Use with four APIs

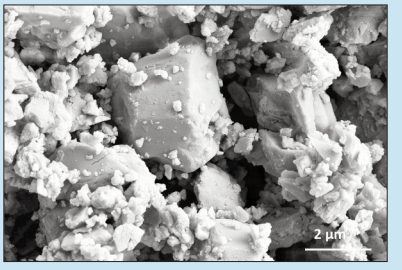
Preisig and et alia studied the feasibility of using a particular grade of FCC (PSD average of 17.9 microns and SSA of 35.43 m^2/g) as a carrier for four poorly water-soluble APIs [2]. The authors studied FCC's loading capacity, the percentage of amorphous drug it could carry, and the dissolution performance when it was combined with ibuprofen (IBU), nifedipine (NF), losartan potassium (LP) and metronidazole benzoate (MB).

The four APIs were dissolved in methanol or acetone and mixed with FCC, and the solvents were then removed using a rotary evaporator that controlled the pressure. Next, the FCC-API particles were loaded with 25 to 50 percent (w/w) of each API in increments of 5 percent (w/w). For reference, the authors also created FCC-API mixtures that contained equivalent API fractions but were not subject to a specific loading strategy, and loading efficiency was assessed using a scanning electron microscope (SEM). The presence of particle agglomerates or drug crystals outside the FCC particles indicated the maximum loading capacity. The authors reported that the particles could accommodate as much as 40 percent (w/w) of API. They also observed a reduction in the interparticle porosity of bulk FCC (63 percent for MB, 58 percent for IBU, 50 percent for NP, and 35 percent for LP), which provided evidence of pore filling. API loading was also quantified by HPLC-UV.

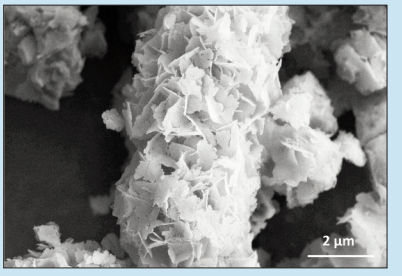
Furthermore, the dissolution rate of the NF and MB was faster for the API-loaded FCC than it was for API-FCC mixtures. Since only low percentages of amorphous NF (8.9 percent) and MB (12.5 percent) were found using differential scanning calorimetry, the authors concluded that the faster dissolution was related to the local increased solubility due to the larger surface area and not to the presence of an amorphous API. Also, the authors concluded that FCC particles could be loaded with APIs and thus used as a drug carrier. In addition, it's possible that the FCC could accelerate the release of certain poorly soluble APIs.

FIGURE 1

Micrographs of natural calcium carbonate and FCC



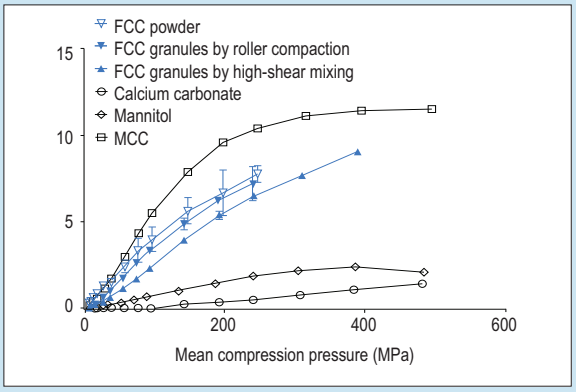
a. Natural calcium carbonate



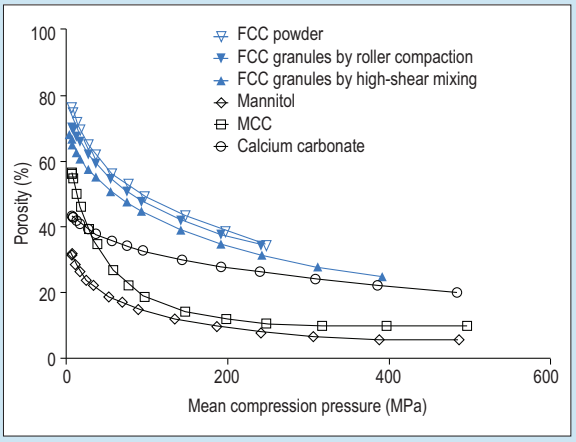
b. FCC, a highly porous structured mineral, is obtained through surface re-crystallization of natural calcium carbonate.

Figure 2

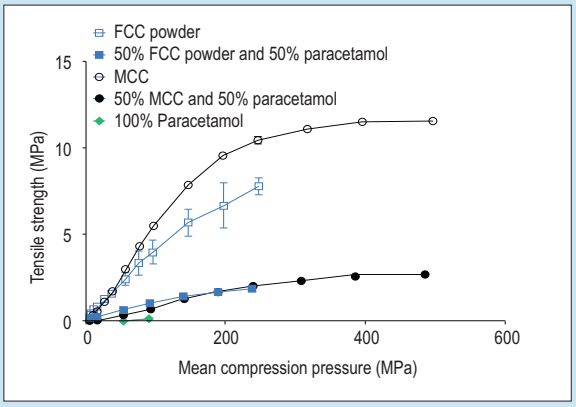
Compression and porosity of tablets made using FCC and reference excipients with and without API [2]



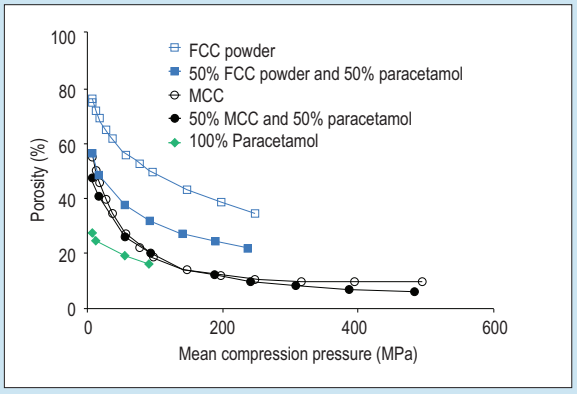
a. Tensile strength versus mean compression pressure for tablets formulated with one of the following: 1) FCC powder, 2) FCC granules by roller compaction, 3) FCC granules by high-shear mixing, 4) calcium carbonate, 5) mannitol, or 6) MCC. At lower compression pressures, FCC tablets reach tensile strengths higher than or comparable to tablets formulated with other reference excipients.



b. Porosity versus mean compression pressure for tablets formulated with one of the following: 1) FCC powder, 2) FCC granules by roller compaction, 3) FCC granules by high-shear mixing, 4) calcium carbonate, 5) mannitol, or 6) MCC. The starting porosity of FCC tablets is higher than tablets formulated with the reference excipients. As compression pressure increases, the porosity of the FCC tablets decreases significantly less than that of tablets formulated with the reference excipients.



c. Tensile strength versus mean compression pressure for tablets formulated with paracetamol and one of the following: FCC powder or MCC. Tensile strength of FCC tablets was comparable to that of tablets formulated with MCC.



d. Porosity versus mean compression pressure of tablets formulated with paracetamol and one of the following: FCC powder or MCC. Despite the presence of an API, as compression pressures increase, the porosity of the FCC tablets decreases significantly less than that of tablets formulated with MCC.

Compressibility

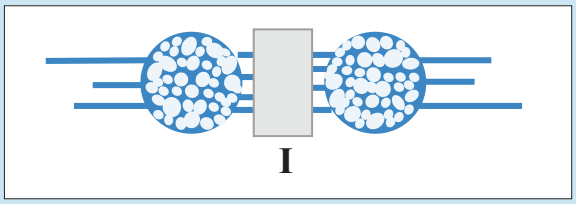
In another study, researchers examined the compressibility of a dry granulation [3]. The resulting granules were used to make tablets that were then compared to tablets made with either FCC in powder form, calcium carbonate, mannitol, or microcrystalline cellulose (MCC).

The researchers then compared the tensile strength and porosity of tablets made across a range of compression pressures (figures 2a and 2b). At low compression pressure, the tensile strength of tablets formulated with FCC powder or granules was higher than that of tablets formulated with mannitol or calcium carbonate and was comparable to that of tablets formulated with MCC. Across the range of compression pressures applied, the FCC tablets had a higher porosity than the tablets made using the other excipients tested. The authors also tested tablets formulated with paracetamol (figures 2c and 2d). The authors concluded that the tensile strength and porosity relationships between tablets formulated with different excipients did not change significantly after paracetamol was incorporated.

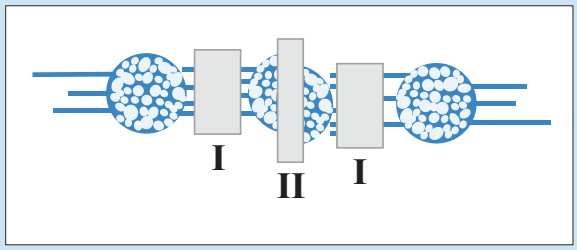
In addition, FCC could be granulated both by high-shear mixing and dry granulation, although the high-shear method would require optimizing because the FCC's lamellae were partially damaged by the 150-rpm impeller and 1,500-rpm chopper that the researchers used. Regardless, with FCC in the formulation, tablets could reach comparable or higher hardness than other formulations at lower com-

FIGURE 3

Compression properties of FCC related to its structure [2]



a. Type I bonds resulting from the interlocking of FCC particles' external lamellae



b. Type II bonds resulting from the deformation by fragmentation of the particles' core

pression pressures, which allowed the porosity to remain higher than 50 percent." That provides a large volume of voids to accommodate APIs.

Furthermore, the authors proposed that the interlocking of the external lamellae—what they called Type I bonds (Figure 3a) —provided a large number of contact points on the surface that lead to greater tensile strengths at lower compression pressures than those of other excipients. At higher compression pressures, the FCC particles deform by fragmentation, yielding new contact points that the authors dubbed Type II bonds (Figure 3b). Finally, the FCC tablets' combination of high tensile strength and high porosity—two desirable but inversely proportional parameters—indicated that FCC could be used in orally disintegrating tablets (ODTs).

Use in ODTs

In fact, one of the first applications of FCC as a pharmaceutical excipient came from Stirnimann et alia, who developed an ODT using it [4]. In order to measure residence time, the authors used a tensiometer in a way that enabled them to measure mass versus time, which in turn allowed them to study water uptake and disintegration kinetics. The authors studied the disintegration kinetics of 24 different formulations and identified four different disintegration patterns (Figure 4). Type I was considered the ideal behavior because it resembled the market formulation, i.e., a gain of mass due to water uptake followed by a loss of mass due to disintegration. Type II was characterized by very fast water uptake but no disintegration, while Type III disintegrated in discrete steps, i.e., tablet pieces. Type IV disintegrated only partially. FCC exhibited a Type I disintegration pattern, and its residence time was half that of the market formulation used as a reference. Furthermore, granules produced by dry granulation using a mixture of FCC and 3 percent (w/w) disintegrant (croscarmellose sodium) disintegrated in 2 seconds (Figure 5a), while ODTs manufactured with the same granules and 10 percent (w/w) caffeine disintegrated in 10 seconds (Figure 5b) [5].

FCC has a high loading capability. It can also produce tablets with high mechanical strength at low compression pressures while preserving internal porosity.

Conclusion

FCC is a very promising new excipient that comprises two monographed minerals. It has high loading capability, and granules can be manufactured by dry granulation. In addition, it can produce tablets of high mechanical strength at low compression pressures, preserving the internal porosity that can be used both for API allocation and fast disintegration. It is exciting to hypothesize what kind of formulations this material will make possible in the near future. FCC could revolutionize ODTs and

FIGURE 4

Types of disintegration kinetics found by testing different ODT formulation options: FCC versus a market formulation. The FCC ODTs disintegrated in half the time [3].

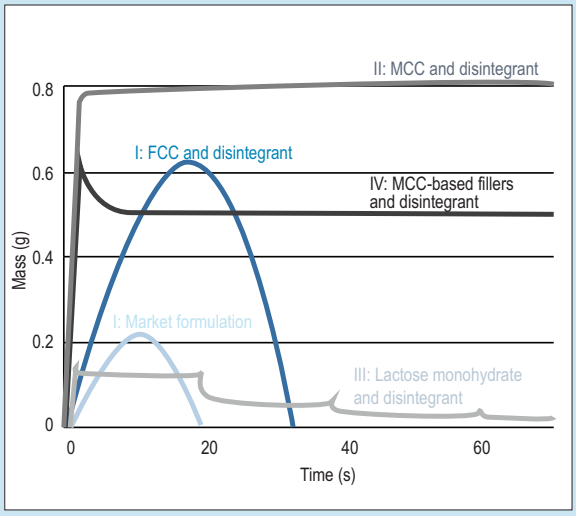
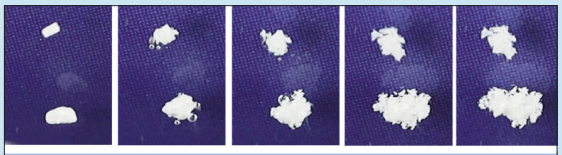


Figure 5

Disintegration of orally dispersible granules (ODGs) and an ODT formulated with FCC [3]



a. ODGs produced by dry granulation from a mixture of FCC and 3 percent (w/w) of disintegrant with a PSD of 180 to 720 microns. The ODGs disintegrated in 2 seconds.

b. ODT manufactured with ODGs and 10 percent (w/w) caffeine. It disintegrated in 10 seconds.

resolve old and new difficulties in formulating pharmaceutical tablets. *T&C*

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