

# The Excipient Challenge

Excipients are defined as any component(s) of a dosage form other than the drug substance. They are added for the purposes of enhancing production, aiding patient acceptability, improving stability and/or controlling release. Moreover, they play an important role in enhancing the processability and bioavailability of drugs by modifying their solubility and/or permeability<sup>1</sup>, which is important information when selecting excipients for any new formulation.

## A Multifunctional Mineral Excipient

Highly porous excipients can help tackle bioavailability limitations of active pharmaceutical ingredients (APIs) by increasing their solubility, e.g. holding the drug in its amorphous, more soluble form within its pores. Omya, a mineral manufacturer, has developed functionalised calcium carbonate (FCC), an excipient with high porosity and compressibility. FCC is manufactured from high-purity natural calcium carbonate which undergoes surface recrystallisation

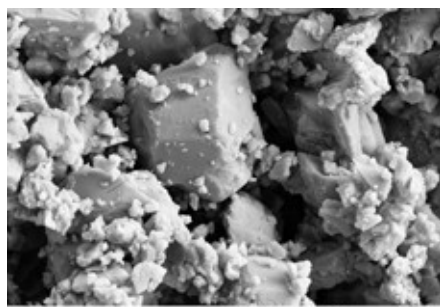


Figure 1: Micrograph of natural calcium carbonate

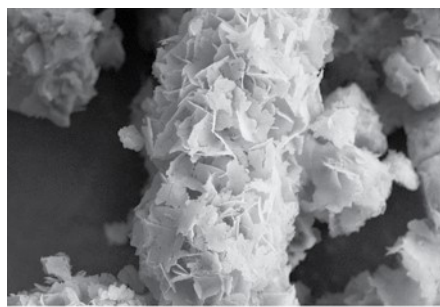


Figure 2: Micrograph of functionalised calcium carbonate

(Figures 1 and 2). This process can be controlled to obtain specific surface areas ranging from 30 to 180 m<sup>2</sup>/g, a median particle size distribution of between 2 and 30 µm, and porosities higher than 60 per cent.

It can be difficult to develop multifunctional excipients that do not multiply the already extensive regulatory burden. FCC offers the advantage of being a structured mineral comprising calcium carbonate and hydroxyapatite, both of which are monographed minerals. The external structure of its particles gives FCC a clear advantage compared to other porous excipients; its external lamellae morphology provides plenty of surface contact points among the particles, ensuring interlocking and enough mechanical strength during dry granulation in roller compactors, in order to be used as a dry binder.

## Tensile Strength vs. Compression Force

Compactibility is the most important functional consideration in the production of a tablet<sup>2</sup>. Therefore, researchers compared tablets manufactured with FCC in powder form and FCC granules with conventional calcium carbonate, mannitol or microcrystalline cellulose (MCC) tablets<sup>3</sup>. The tensile strength and porosity of the tablets were analysed across a broad range of compression forces. At low compression forces, the tensile strength of tablets formulated with FCC powder or FCC granules was higher than that of tablets formulated with mannitol or calcium carbonate and was comparable to that of tablets formulated with MCC (Figure 3). The FCC tablets also had a higher porosity than those containing the other excipients tested.

With FCC in the formulation, tablets were able to reach comparable or higher hardness at lower compression forces than other formulations. This allowed their porosity to remain higher than 50 per cent and provided a large volume of voids in which to accommodate APIs.

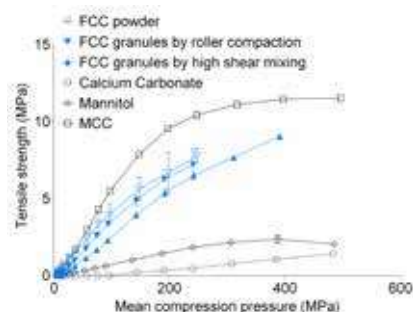


Figure 3: Tensile strength vs. mean compression force for tablets made using FCC and reference excipients. At lower compression forces, FCC tablets reach tensile strengths that are higher than or comparable to those of tablets formulated with other reference excipients.

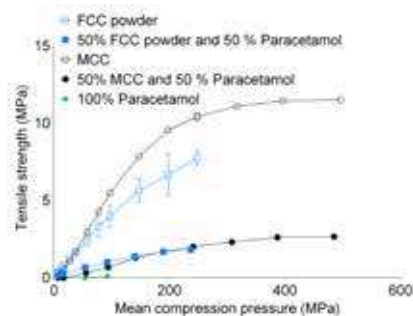


Figure 4: Tensile strength vs. mean compression force for tablets formulated with paracetamol and one of the following: FCC powder or MCC. The tensile strength of FCC tablets was comparable to that of tablets formulated with MCC.

In a second step, the researchers analysed tablets formulated with paracetamol and one of the following: FCC powder or MCC. They concluded that despite the presence of an API, the decrease in porosity of the FCC tablets was significantly less than that of tablets formulated with MCC when compression force was increased. Additionally, the tensile strength of the FCC tablets was comparable to that of tablets formulated with MCC (Figure 4). Finally, the FCC tablets' combination of high tensile strength and high porosity indicated that FCC is suitable for the preparation of solid oral dosage forms.

## Fast Disintegration

Using a tensiometer in order to simulate residence time of a tablet in the mouth, another research group analysed the disintegration kinetics of 24 different formulations<sup>4</sup>

and identified four patterns. Type I was considered the ideal behaviour because it resembled the market formulation. Type II was characterised by very fast water uptake but no disintegration. Type III disintegrated in discrete steps, resulting in tablet pieces, while type IV disintegrated only partially. Tablets formulated with FCC and croscarmellose sodium exhibited a type I disintegration pattern, and their residence time was one half that of the market formulation used as a reference.

FCC provides a solution that combines good compactibility with fast disintegration. Thus, it can also help to tackle challenges in the formulation of orally disintegrating tablets (ODTs). From the perspectives of cost and simplicity, the preferred method of preparing ODTs is direct compression. However, the disintegration capacity of ODTs produced in this way is limited by the hardness of the resulting tablets<sup>5,6</sup>. Therefore, when compressing ODTs, the main challenge is manufacturing a tablet that enables fast disintegration without compromising on its mechanical stability. This requires an excipient that offers optimum cohesiveness for compaction.

It was FCC's direct compressibility into granules without the use of a binder and its high porosity that allowed faster water uptake, which led to a disintegration time that was twice as fast as the market reference product. In fact, granules manufactured with FCC disintegrate in 2 seconds and their corresponding ODTs in less than 10 seconds.

In a recent study<sup>7</sup>, scientists investigated the use of FCC to formulate ODTs with enhanced mouthfeel. It was shown that the tablets were well accepted by healthy volunteers. Mouthfeel was successfully enhanced to a pleasant result without losing the characteristics of FCC: the high compactibility and the resulting physical stability of tablets, plus the high porosity responsible for the fast liquid absorption necessary for the rapid tablet disintegration.

### Loading Capability

FCC particles can also be loaded with certain APIs and can thus be used as drug carriers.

Researchers at the University of Basel in Switzerland investigated the feasibility of using a particular grade of FCC as a carrier for poorly water-soluble APIs. Ibuprofen (IBU), nifedipine (NP), losartan potassium (LP) and metronidazole benzoate (MBZ) were selected as model substances with which to investigate drug loading<sup>8</sup>. The team analysed the loading capacity of FCC, the dissolution performance and whether the drug was loaded in its amorphous or crystalline form. The four APIs were dissolved in methanol or acetone and mixed with FCC. Using a rotary evaporator to evaporate the solvent under reduced pressure, the FCC-API particles were loaded with 25 to 50 per cent (w/w) of each API. For reference, the scientists also created FCC-API simple blends that contained equivalent API fractions but were not subject to a specific loading strategy. Loading efficiency was assessed using a scanning electron microscope. The presence of particle agglomerates or drug crystals outside the FCC particles indicated the maximum loading capacity was exceeded. It was shown that FCC particles can be successfully loaded with up to 40 per cent (w/w) API. The team also observed a reduction in intraparticle porosity after drug loading (63 per cent for MBZ, 58 per cent for IBU, 50 per cent for NP and 35 per cent for LP), which provided evidence of pore filling. In addition, the dissolution rate of FCC loaded with NP and MBZ was found to be faster than that of the FCC-API mixtures. Since only low percentages of amorphous NP (8.9 per cent) and MB (12.5 per cent) were detected, the authors concluded that the faster dissolution was related to the locally increased solubility caused by the larger surface area and not to the presence of an amorphous API.

A recent study shows that FCC is also a suitable excipient for the delivery of proteins<sup>9</sup>. In this work, FCC was loaded with biomolecules such as lysozyme and bovine serum albumin in order to investigate its suitability for delivering protein-based drugs. Delivery of biologics, such as therapeutic proteins, critically depends on the availability of formulation strategies that can be used to deliver these macromolecules to target

tissues. The structural and functional integrity of the biologics also have to be preserved during manufacturing and storage. Loading efficiency for the study's model proteins was more than 90 per cent. The structure of both model macromolecules was not affected by the loading process or the interaction with the surface of FCC as confirmed by circular dichroism analysis. Moreover, enzyme activity of both model proteins after loading was demonstrated by Michaelis-Menten enzyme kinetic experiments.

### Outlook

Several studies have shown that FCC is a versatile carrier with unique properties and processability. With this natural mineral excipient, fast disintegrating tablets, granules, floating and mucoadhesive drug delivery systems as well as microencapsulated products can be developed.

ODTs manufactured with FCC do not require cost-intensive production equipment because they can be produced by direct compression of dry granulated FCC with the active of choice. The high mechanical strength of ODTs formulated with FCC enables the use of regular bottles and blisters as packaging, which significantly reduces the overall cost of production compared to other ODT technologies.

FCC offers multiple functionalities with very simple chemistry and a straightforward granule and tablet manufacturing process. Additionally, it is possible to tailor the characteristics of FCC, such as specific surface area, particle and pore size distribution, according to the requirements of various applications. Furthermore, unlike many similar materials, FCC has the advantage of being highly biocompatible. Its composition is basically that of bone material: hydroxyapatite and calcium carbonate. Also, from a regulatory point of view, FCC has advantages: it is a co-processed excipient composed of only two monographed minerals.

Bearing all of these advantages in mind, FCC is a very promising excipient for dry oral dosage forms. It will be interesting to see what kind of formulations this mineral will make possible in the near future.



## REFERENCES

1. Elder D.P. et al.: Pharmaceutical excipients – regulatory and biopharmaceutical considerations. *Eur. J. Pharm. Sci.*, 87, 88–89. 2016.
2. Levin. *Pharmaceutical Process Scale-Up* (2001), CRC Press.
3. Stirnimann T. et al.: Compaction of functionalized calcium carbonate, a porous and crystalline microparticulate material with a lamellar surface. *Int J Pharm.* 2014; 466 (1-2): 266–75.
4. Stirnimann T. et al.: Functionalized calcium carbonate as a novel pharmaceutical excipient for the preparation of orally dispersible tablets. *Pharm Res* 2013; 30 (7): 1915–25.
5. Sreenivas S.A.: Orodispersible tablets: new-fangled drug delivery system – a review. *Indian J Pharm Educ Res.* 2005;39(4):177–81.
6. Kumar V.D. et al.: A comprehensive review on fast dissolving tablet technology. *J App Pharm Sci.* 2011; 1(5):50–8.
7. Wagner-Hattler L. et al.: In vitro characterization and mouthfeel study of functionalized calcium carbonate in orally disintegrating tablets. *Int J Pharm.* 2017 Dec 20;534(1-2):50–59.
8. Preisig D. et al.: Drug loading into porous calcium carbonate microparticles by solvent evaporation. *Eur J Pharm Biopharm.* 2014; 87: 548–58.
9. Roth R. et al.: Functionalized calcium carbonate microparticles for the delivery of proteins. *Eur J Pharm Biopharm.* 2018 Jan;122:96–103.



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