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Excipients for Hard-shell Capsules: Why Cellulose is Not Enough

Excipients are essential ingredients for a solid oral dosage form's good performance, ensuring correct bioavailability, solubility, stability and dose accuracy. Therefore, choosing the right excipient is paramount for the adequate clinical performance of a robust dosage form. This choice needs to be based on technical parameters of both the active pharmaceutical ingredient (API) and the functionality of the dosage form itself – therefore science needs to be on the backbone of such process.

As an example of the importance of the excipient's role on the dosage form performance, we can consider the case of an intoxication that occurred in Australia in the late 1960s: epileptic patients who were taking phenytoin capsules experienced intoxications due to the replacement of the diluent. Calcium sulphate was changed to lactose, and this led to an increase of the mean serum concentration of phenytoin (a narrow therapeutic index drug) resulting in toxicity due to increased exposure. This difference was suspected to be the result of calcium sulphate converting some of the phenytoin into an unabsorbable or poorly absorbed form of the drug, an effect that did not occur with the lactose excipient. This example demonstrates that properties such as bioavailability and stability of the dosage form may be dependent on the use of the right excipient.

Another important factor when discussing excipients is the pharmaceutical handling of the powders during hard-shell capsules preparation, i.e., the excipients play roles both on clinical performance and on pharmaceutical technology. One can say that the main factors influencing the properties of powders and the consequent filling of hard-shell capsules are powder flow, tapped powder density (maximum density without applying a major compressive force), powder compressibility, powder adhesiveness, and cohesiveness. The

free flow of a powder is the most important factor for the uniform filling of capsules, and it directly influences the quality of the product, for example, in weight and content uniformity. To obtain a good flow powder formulation, a free-flow diluent and a glidant are typically used.

Cellulose derivates such as microcrystalline cellulose are some of the most commonly used excipients worldwide. In fact, cellulose has been used as a pharmaceutical excipient since the 1950s. It is a fine powder that can be used as a diluent and a disintegrant. However, it has poor flow properties. In an attempt to improve the characteristics of cellulose, several modifications have been made. Among them is one that led to microcrystalline cellulose (MCC), in which part of the α-cellulose undergoes depolymerization by acid hydrolysis to remove the amorphous cellulose fractions, producing microcrystallized particles. To achieve a deformable powder, cellulose is washed, disintegrated into small fragments, and then submitted to a spray-drying process.

Microcrystalline cellulose is characterized by its high crystallinity (60%–80%) and low molecular weight. The degree of crystallinity is important due to its influence on various properties, including compression and water absorption, directly interfering with the flow and stability of the finished product. MCC chemical composition and structure depend on the raw material used and the production conditions. As a result, several types of MCC are available on the market with different particle sizes, crystallinity, morphology, and water content, resulting in different functional parameters and applications.

Although MCC improved the flow of cellulose, making it more adequate to be used as a diluent for capsules, its use standalone is yet not optimal to provide full functionality to an excipient. The addition of other excipients to MCC should be considered to provide a better performance. For example, a mixture of MCC and pregelatinized starch, in an amount corresponding to at least 50% of the formulation, may be appropriate to prevent problems with low melting point substances. Also, powders with a tendency to absorb moisture should not be mixed with excipients containing a large amount of water, such as cellulose and starch – absorbent excipients or moisture-regulating excipients, such as anhydrous lactose or mannitol, are preferred in this situation.

Those examples highlight the need for an optimized excipient that can act both as diluent/filler and as an adjuvant for the compounding of the dosage form and the solubility of the API. This is because the powder flow is only one of the multiple characteristics that should be evaluated when choosing an excipient for capsules. Some of the parameters that need to be considered during this excipient-selection process include the API stability profile, the API-excipient compatibility, powder flowability and packing, powder mixing process and its critical factors, disintegration and dissolution rate, powder hygroscopicity, desirable release profile, patient adherence and API bioavailability profile.

Regarding drug bioavailability and its relationship with capsules formulation, the Bio-pharmaceutical Classification System (BCS) is a useful tool for the standardization and automatization of the decision process for excipients. The BCS scheme was designed to correlate in vitro drug product dissolution and in vivo bioavailability, based on two criteria: drug dissolution (solubility) and gastrointestinal permeability, which are the fundamental parameters controlling rate and extent of drug absorption.

The knowledge gained from the BCS can help us to understand how to improve bioavailability of solid oral formulations by adjusting the excipient composition. This knowledge was the base for the development of our DiluCap capsule fillers line. DiluCap fillers not only provides good flow properties but also the adequate solubility/dissolution of the hard-shell capsule formulation, enabling the API to permeate at its fullest. DiluCap represents the next-generation of excipients for capsules, providing extra functionalities that the use of MCC standalone would not be able to fulfil.

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