The Selection of Excipients for Oral Solid Dosage Forms

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Introduction

The preferred route of administration for most Active Pharmaceutical Ingredients (APIs) is orally due to ease of administration, improved patient adherence and reduced complexity required to manufacture oral solid dosage forms compared with alternative drug delivery systems. Factors which may preclude oral administration of APIs include poor bioavailability resulting from poor solubility and/or permeability, poor stability and degradation during gastric transit, as well as the therapeutic site and method of action. Examples of common oral solid dosage forms include tablets, capsules, beads, orally disintegrating tablets (ODTs) and lozenges, all of which involve compounding the required quantity of the API (the dose) with one or more excipients. The range of excipients available to the formulator is truly diverse; however, excipients are, in general, intended to be pharmacologically inert whilst conferring advantageous physical properties to the formulation, facilitating its ability to safely and reliably deliver the API to the therapeutic site of action. Excipients are only included within a formulation if there is suitable justification to do so. In general, the selection of an excipient is based on the dose, type of drug product, physicochemical properties, chemical compatibility with the API, route of delivery, administration frequency, interactions with other formulation components, method of manufacture, processability and the container or closure system.[1] This chapter aims to describe the scientific rationale behind the selection of common excipients used to manufacture oral solid dosage forms.

Excipients to enhance the flow of powders and granules

One of the most commonly identified critical quality attributes (CQAs) in the production of oral solid dosage forms is powder or granule flow. Modern tablet and capsule machines are designed to produce several hundred thousand units per hour and adequate flow of the final blend is essential to ensure that the resultant dosage form is consistent in terms of weight, composition and, for tablets, the degree of compaction it has received.

Flowability is not an inherent powder property but depends on four factors:

- Intrinsic properties such as particle size, density, shape and roughness.
- Bulk properties such as particle size distribution, cohesive and frictional interactions.
- External conditions such as temperature, humidity or state of compaction.
- Processing equipment design and settings, which affect the powder dynamics.

As such, it is impossible to adequately characterize flow using a single measurement technique. Although traditional, empirical tests such as compressibility or angle of repose may give a qualitative means of classifying or comparing powder behaviors, the data produced by more sophisticated techniques such as ring shear testing or powder rheometry enables a more complete characterization of powder flow and cohesion properties.[2]

APIs are often subjected to a particle size reduction process in order to ensure that the final dosage form meets the required standards of content uniformity and dissolution; thus they often contain a significant proportion of fine particles (e.g. with diameter <20 μm). These particles, by virtue of their high specific surface area, often exhibit high degrees of adhesion to other surfaces and cohesion to neighboring particles resulting in poor flow.[3] Certain morphologies of the API such as needle-shaped or acicular particles may also have a negative impact on flow due to mechanical locking. As a result, where the formulation contains a high percentage of API (e.g. $>10\%$) it may be possible to improve the overall blend flow by modifying either the particle shape or the particle size of the API present.

If the formulation composition is fixed, a preferred option for improving flow is to increase the particle size using a granulation process, which requires a degree of compactibility and moderately good flow for the purposes of roller compaction or the selection of an appropriate binder if wet granulation is adopted. If the formulation is open to modification, flow can be improved by switching excipient grades; many of the excipients used in solid dosage forms are marketed in a range of different particle size grades as shown in Table I. The benefits of increasing particle size must be weighed against the potential increased risk of API segregation from the other blend components, or the possible reduction in compactibility or dissolution rate. For example, one of the larger grades of microcrystalline cellulose (*Avicel PH-200*) has improved flow but has poorer compactibility than a smaller particle size grade (*Avicel PH-102*).[4]

The flow of both powders and granules can often be significantly improved by the addition of glidants, which are very finely divided powders that, by virtue of their small particle size (typically less than 50 nm), have a strong tendency to become adsorbed onto the surface of larger powder blend components. This process increases the minimal contact distance and reduces the contact area between the larger particles, resulting in the reduction of van der Waals forces and the tendency of powders to aggregate.[5,6] Additionally, glidants may increase flowability by absorbing moisture or rolling under stress.[5] Colloidal silica is one of the most effective glidants and is usually added at levels $<1\%$, but other materials such as maize starch or talc are often used in capsule formulations where compactibility is less crucial. A recently developed technique to improve flow known as 'nanocoating' involves comilling of colloidal silicon dioxide onto host pharmaceutical particles, prior to the addition of the remaining formulation components. This step has been shown to improve the flow of both APIs and active blends.[7]

Excipients to enhance the compaction of oral solid dosage forms

Compaction can be defined as the transformation of a powder or granules into a coherent dosage form of defined shape through the process of compression[8] and is the fundamental concept behind successful tablet production. A degree of compactibility is also important for capsule formulations, as successful capsule filling depends on the production of robust and uniform powder plugs at forces much lower than those used in tablet production.[9]

The compaction of a powder under pressure generally involves a number of processes:[8]

- Particle rearrangement