excipients can have a large effect on disintegrant action, particularly at a lower or higher pH.

Wet and dry granulation processes may extend tablet disintegration times by increasing the disintegrant particle size; the modified cellulose types may be less susceptible to this effect, and dry granulation is likely to have a lesser effect than wet granulation.[23] Where a formulation requires granulation, it is sometimes necessary to incorporate disintegrants in both the intra- and extra-granular locations.[24] Some excipient manufacturers offer alternative grades of disintegrants that are recommended for granulated formulations.

Excipients to facilitate the granulation of oral solid dosage forms

Where the drug loading exceeds approximately 30%, or where the physicochemical properties of the API may be expected to significantly change the physicochemical properties of the formulation, it may be preferable to adopt a granulation process that renders the formulation less dependent on the API properties by:

- Improving the uniformity of API distribution.
- Improving the distribution of functional excipients e.g. disintegrants.
- Increasing density and flow.
- Reducing dust.

Techniques for granulation can be broadly divided into wet and dry methods. In wet granulation a binder solution is added, usually by spraying into the powder blend whilst mixing, either under low or high shear conditions. The wet mass is dried and then milled, prior to the addition of additional excipients such as lubricants. The water absorbing qualities of MCC make it particularly suitable for the wet granulation process, although some of its compactibility may be lost during the process, so it is common to combine it with a brittle fracturing excipient in order to maintain tablet hardness. The wetting and drying process may also compromise the efficacy of some disintegrants so care should be taken when making selections for which to use.

Binders are used in wet granulation to promote the agglomeration of powders into granules; they may also improve tablet hardness by enhancing both intragranular and extragranular forces. A wide variety of natural and synthetic polymers and sugars have been used in wet granulation as shown in Table III.[25]

Table III: Commonly used binders for wet granulation.

Natural Polymers	Acacia; alginic acid; gelatin; sodium alginate; starch.
Synthetic polymers	Carboxymethylcellulose sodium; ethylcellulose; hypromellose; methylcellulose; povidone.
Sugars	Dextrose; sucrose; sorbitol.

The natural polymers and sugars are generally added to the powder blend in the form of a solution or, in the case of starch, as a paste; the synthetic polymers may be added as a dry powder, a solution in water, or a hydroalcoholic solvent blend. Whilst the selection of a binder may be affected by experience and precedence, it should largely be determined through optimization studies using parameters such as granule and tablet friability, tablet tensile strength, dissolution and stability.

Dry granulation is usually achieved via the process of roller compaction, where the powder is compressed between two counter-rotating rollers; thus formulations designed for roller compaction must possess good compaction properties as well as sufficient flow to maintain a consistent process. The ribbons or flakes formed are then milled to the required size. Roller compaction is generally a faster process, and, because it avoids the wetting and drying steps involved in wet granulation, it is suitable for moisture and heat sensitive APIs or excipients.[25] As the forces involved in roller compaction are only slightly less than those involved in tablet compaction, the tensile strength of the final tablets will be reduced compared to tablets prepared from the original powder blend. Some of the compactibility of roller compacted granules may be improved by the addition of extra-granular MCC or a polymeric binder.[14,15] Tablet tensile strength may also be improved by the selection of smaller particle size grades of excipient (e.g. MCC), as the poor flow of these materials is ameliorated by the granulation process.[26]

Excipients to enhance the bioavailability of APIs within oral solid dosage forms

The physicochemical properties of both the API and the formulated medicine, including the *in vivo* solubility and permeability, will determine the pharmacokinetic parameters and the absolute bioavailability of the API. According to the biopharmaceutics classification system (BCS) as adopted by the FDA, APIs may be broadly divided into four main classes depending on their solubility and permeability as shown in Figure 1.[27] In this instance, the solubility refers to the solubility of the API in aqueous media over a pH range of 1 to 7.5 and the permeability relates to the permeability of the API through the intestinal wall.[27]

BCS Class II and Class IV compounds, which have low solubility, may be poorly bioavailable since the API does not readily dissolve in gastrointestinal (GI) fluid. In this case, the dissolution rate is the rate limiting step for systemic absorption, which may reduce the ability of the API to be therapeutically active, even at high doses.

A number of techniques may be used to improve the solubility of the API particles and the bioavailability, including particle size reduction, polymorph and salt selection, and surface chemistry modification.[28] Excipients may also be used to further enhance the solubility via a number of different mechanisms.

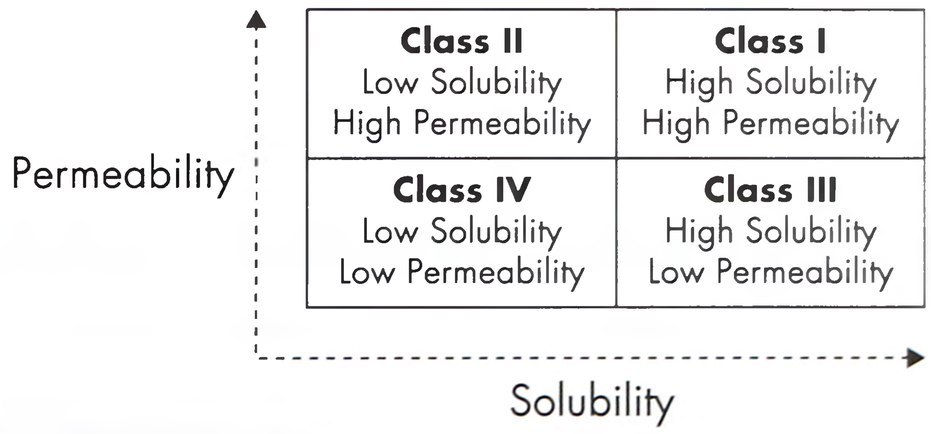

Figure 1: The biopharmaceutics classification system (BCS) as determined by the permeability and solubility of active pharmaceutical ingredients according to FDA guidance.[27]

Cyclodextrin Complexation

Cyclodextrins are cyclic oligosaccharides which are obtained from the enzymatic degradation of starch. The most commonly used are α, β and γ-cyclodextrins, which are cup shaped and consist of a ring of 6, 7 or 8 D-(+)-glucopyranose units respectively. The external surfaces of cyclodextrins consist of polar, hydrophilic, water soluble functional groups that impart water solubility. The internal cavity consists of apolar, hydrophobic groups that are able to complex to the API, and the cyclodextrin is chosen so that the diameter of the internal cavity matches the diameter of the API for complexation. Cyclodextrin–API complexes may be prepared by generating solutions which are subsequently spray-dried or freeze-dried to produce the complex as a solid powder. Substituted cyclodextrin complexes are commonly used in parenteral formulations. Cyclodextrin complexes may also be included in oral solid dosage forms, and as well as improving API solubility and bioavailability, they may also improve API stability, taste, odor and other physical properties.[29]