Table I: Examples of particle size grades of common solid dosage form excipients.

Excipient	Grade	Manufacturing method	Nominal particle size (μm)
Microcrystalline cellulose	*Avicel PH-101*	Spray Dried	50
	Avicel PH-102	Spray Dried	100
	Avicel PH-200	Spray Dried	180
α–Lactose monohydrate	*Fast Flo*	Spray Dried	120
	Tablettose 70	Spray Agglomeration	200
	Tablettose 80	Spray Agglomeration	180
	FlowLac	Spray Dried	190
Dibasic calcium phosphate anhydrous	*A-TAB*	Precipitation	180
Starch, pregelatinized	*Starch 1500*	Partial pre-gelatinisation	65
Corn starch and pregelatinized starch, coprocessed	*StarCap 1500*	Partial pre-gelatinisation & blending with corn starch	90
Mannitol	*Pearlitol 50 C*	Crystallization	50
	Pearlitol 200 SD	Spray Dried	180

- Elastic i.e. reversible deformation of particles
- Plastic i.e. irreversible deformation of particles
- Fragmentation of particles
- Formation of interparticle bonds

Theoretically, materials may compress by either plastic deformation or brittle fracture but, in practice, most excipients and drugs will compact via a combination of these mechanisms. Compacts prepared from the excipients most commonly used to formulate immediate release dosage forms can be ranked in order of tensile strength as follows:[10]

Highest

Microcrystalline cellulose

Spray-dried lactose

Dibasic calcium phosphate

Lactose

Mannitol

Lowest

A number of particle bonding mechanisms that may occur during compaction have been identified however, three tend to dominate where dry powders are involved:

- Solid bridges (e.g. due to melting)
- Distance attraction forces (intermolecular forces)
- Mechanical interlocking (between irregularly shaped particles)

Intermolecular forces act between surfaces separated by distances of 100–1000 Å and are the dominant bonding mechanism for plastically deforming materials.[8] If the surfaces of these particles become coated with the API or a lubricant, such as magnesium stearate, the bonding ability can be seriously compromised. However, during the compaction of brittle materials, fresh uncoated surfaces are exposed by particle breakage and for this reason it is generally preferable to formulate tablets using a blend of plastic and brittle materials in order to maintain tablet hardness despite changes in processing methods or API properties. Solid bridges are formed where a true contact is established between particles at the atomic level. These can occur as a result of sintering, melting, crystallization, chemical reaction or binder hardening. Mechanical interlocking can occur when particles become twisted or hooked together and thus depends on the shape and surface structure, becoming more significant where needle-shaped fibers or irregular particles are compressed.[9]

Microcrystalline cellulose (MCC) is partially depolymerized cellulose comprised of needle-like microcrystals agglomerated into porous particles. As a result of its peerless compactibility, low lubrication requirement and self-disintegrating properties, MCC has become perhaps the most popular excipient for tablet compaction in the modern pharmaceutical industry.[11,12] A range of grades is available that vary in their particle size, moisture content, and density and therefore their physical properties and applications. In order to avoid potential segregation issues in blends destined for direct compression, it is advisable to use a grade of a similar particle size to the API being formulated. MCC also exhibits a high degree of viscoelastic behavior, resulting in increased strain rate sensitivity; hence at higher tableting speeds there may be insufficient time for plastic deformation to occur and care is needed when scaling up formulations containing MCC from slow speed development presses to high speed rotary production machines.[12]

Lactose is widely used as a tablet excipient and is available in several grades with differing physical properties. Spray-dried lactose comprises mainly of α–lactose monohydrate microcrystals bound into spherical agglomerates by small amounts of amorphous lactose, and was specifically designed to exhibit the superior flow and compaction properties necessary for direct compression.[11]

Dibasic calcium phosphate dihydrate forms very hard but brittle compacts and is frequently used in tandem with plastic materials such as MCC; blends formed can therefore be used for both direct compression and granulation. It has a high bulk density, which can lead to segregation issues with some APIs, but an anhydrous form of lower density is available as well as granulated grades possessing superior flow.[13]

Mannitol and sorbitol both have good aqueous solubility, a pleasant cooling taste, and are widely used in the manufacture of chewable and sublingual tablets.[11] Although mannitol contributes little in the way of strength to a tablet, it does show a reduced tendency for brittle fracture making it suitable in direct compression applications.[10] Mannitol may also be an appropriate replacement for lactose, where the latter shows chemical incompatibility with the API. The hygroscopic nature of sorbitol may accelerate the degradation of moisture-sensitive compounds, and recrystallization of sorbitol upon ageing may also give rise to tablet hardening over time.

Pregelatinised starch is a form of starch which has been chemically and/or mechanically modified to rupture some of the starch granules; this process improves the compactibility, disintegration and flow. This material, however, is sensitive to the adverse effects of magnesium stearate on tablet hardness and dissolution; hence stearic acid may be a better choice of lubricant. At higher strain rates, starch deforms elastically which can increase the risk of tablet capping.[11]

In addition to the fillers mentioned above, low levels (<10%) of a high performance dry binder (e.g. polyethylene glycols or povidones) may be added to a formulation to increase compactibility either for tableting or as an aid to granulation by roller compaction, without significantly adding to the tablet weight.[14,15]

Various excipient grades are commercially available with a range of properties, and it is essential that the correct grade is identified as