For a wide range of drugs, tablets are the preferred form of delivery. There are many reasons for this preference. Tablets have a high level of patient acceptability and compliance because they provide an accurate dosage and are easy to swallow. The form is distinctive and identifiable as tablets come in a variety of shapes and colors and readily accept debossing techniques. Due to their low moisture content, tablets possess satisfactory physical and chemical stability. In addition, they taste bland, are less prone to tampering than other dosage forms, are convenient for packing, shipping and administering and offer advantages in manufacturing speed and cost.

That said, tablets also possess some disadvantages, when compared to other delivery forms. First and foremost, there is a potential for bioavailability problems as dissolution must precede absorption. Tablets for immediate release should disintegrate rapidly (less than 10 minutes) after ingestion in order to facilitate solution of the drug. Of course, gastrointestinal irritation can occur due to a locally high concentration of the drug and some patients report swallowing difficulty, so size and shape becomes important (round @ 200mg).

Before detailing the tabletting technology, it is important to review some common definitions that play pivotal roles in production.

Compressibility: The ability of a material to undergo a reduction in volume as a result of an applied pressure. It is represented by a plot showing the reduction of tablet porosity with increasing compaction pressure. The lower the porosity at a given compaction pressure, the better is the compressibility and the greater is the inter-particulate bonding area in a tablet.

Tabletability: The capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure.

Compactibility: The ability of material to produce tablets with sufficient strength under the effect of densification. In many cases, the tensile strength of a tablet decreases exponentially with increasing porosity.

An Array of Tablet Types

Besides understanding the above-mentioned production terms, it is also important to be aware of the various types of tablets that are currently on the market.

Immediate Release Uncoated Tablets: Usually no taste/stability issues.

Coated Tablets: For taste/stability/identification (coated with water-soluble/dispersible polymer–mixture of hydroxypropyl cellulose/hydroxypropylmethyl cellulose); coating readily ruptures in GI tract.

Enteric-Coated Tablets: For drugs inactivated or destroyed in the stomach or for those
causing irritation to the gastric mucosa; tablet passes through the stomach but disintegrates in the intestines where absorption takes place. Excipients used for enteric coating include cellulose acetate phthalate, mixtures of fats and fatty acids, etc.

Multiple Compressed Tablets: Multiple-layered tablets manufactured by using more than one compression cycle. Each layer contains a different drug and each may be colored differently.

Controlled Release Tablets: Improved therapy, less toxicity, improved patient compliance—using polymers such as methacrylates.

Sublingual Tablets: Small, flat ovals such as nitroglycerin. They are ideal tablets for absorption of drugs which are destroyed by gastric juice or undergo first pass metabolism.

Chewable Tablets: Disintegrate rapidly when chewed for patients with swallowing difficulty (children, elderly) and when there is no access to water. Most commonly used for multiple vitamins and antacids.

Effervescent Tablets: In addition to the active, this product form contains sodium bicarbonate and citric acid. When water is added the ensuing chemical reaction forms carbon dioxide, which acts as a disintegrant and produces effervescence that hastens dissolution (antacids).

Once the formulator (and the marketing department) has finalized the product form, there are several steps required to produce a tablet. These include:

Compression: Reduction in bulk volume of the material in the die as a result of removing entrapped air;

Consolidation: Particle/particle interaction giving rise to increased mechanical strength;

Decompression: Removal of the load placed upon the punches (axial stresses); and

Ejection of the Tablet: Removal of the tablet from the die (radial stresses).

Initial loading of the punches during compression causes the powder bed to form a closely packed structure due to rearrangement. Upon continued loading during the consolidation process, the particles may undergo elastic and plastic deformation, particle fracture, inter-particulate bonding, both inter-particulate and particle-die wall friction, or all of the above.

Which Production Method is Best?

Formulators can choose from a wide range of manufacturing methods—including wet granulation, direct compression (DC) and dry granulation—to produce tablets. Several of
these methods, along with their pros and cons, are detailed below.

Wet granulation is a production method that is widely favored by pharmaceutical manufacturers. Using this method, formulation compressibility and content uniformity increases. At the same time, the binder increases particle strength, and particle size and shape are optimized for flow. Furthermore, dustiness is decreased due to improved handling; the tablet can be dried to low final moisture content and segregation of fines can be prevented. Using wet granulation, hydrophobic drugs wet better due to the incorporation of the binder, the coalescing of particles locks in blend uniformity compressibility and consolidation is improved by using the appropriate binder and maintaining the correct moisture content of the granules.

Of course, there are several disadvantages with wet granulation. For example, the procedure features a large number of process steps—making it more expensive (labor/time) and complicated than other methods. Wet granulation also exposes labile drugs to moisture and heat conditions and there is some material loss during processing. Assay and dissolution problems can occur if the drug (especially low dose) forms complex with the binder, or are adsorbed onto one of the other excipients.

Direct Compression: Pros & Cons

In contrast to wet granulation, direct compression methods are rather simple. In fact, the two-step process, involving screening and/or milling and final mixing, can often save labor, time, equipment and space. It is ideal for simple formulation. Since the technique requires neither heat nor moisture, direct compression also enhances stability. Force feeders and better compressible excipients have made this process very popular in recent years.

At the same time, direct compression is not suitable for high-dose drugs that have poor compression and flow properties. Furthermore, drugs with extremely low bulk density are difficult to compress directly due to air entrapment. They are also sensitive to over-lubrication and there is a limit to color variation. Moreover, there is often non-homogeneous distribution of low-dose drugs due to segregation after blending (content uniformity). Direct compression calls for commensurate particle size or particle size distribution between drug and excipients.

Dry Granulation: Pros & Cons

Dry granulation may be viewed as a pre-compression process that takes place off the press to provide added flexibility of dwell time and compression force. It offers better stability than wet granulation and it works when direct compression is not possible. It also improves the flow property by increasing the particle size. Direct compression also increases the density of low-density drugs. It decreases the elastic recovery of some compounds, thereby increasing final compactability. Bonds are formed with moderate compressibility.
However, dry granulation may require recycling or reprocessing and therefore may adversely affect batch control (friability and dissolution). There is also the possibility of color variation and segregation during finished mixing.

A Closer Look at Wet Granulation

Wet granulation has several objectives. In addition to increasing particle size and flow, compressibility and densification, wet granulation also produces generally spherical, uniform-sized particles with hydrophilic surfaces and uniform distribution of the drug and the advantage of covering the raw materials in a sea of binder paste.

Stages of wet granulation include:

• Agglomeration;
• Agglomeration breakdown;
• Re-agglomeration; and
• Paste formation.

However, if paste formation occurs, then the conventional end-point of granulation has been passed. There are several methods of detecting granulation endpoints, including mixing time, current or power increase, motor speed variation, torque change and product temperature. There are also several ways to assess granule properties including loose (bulk) density; i.e., pouring granules into a 100-ml glass cylinder and density = weight/volume. In the tapped density assessment, the granule density is measured after tapping for about 2000 taps.

The Carr Index is obtained by the formula:

Tapped density-Bulk Density/Tapped Density x 100

To obtain a Hausner Ratio, the bulk density is divided by the tapped density. Low values for both indicate good flowability. In other words, the more the powder can be densified, the lower its flowability.

Here’s how to figure out the Carr Index:

• Excellent flow: 5-15%;
• Good flow: 12-16%;
• Fair flow: 18-21%;
• Poor flow: 25-35%; and
• Very poor: 33-38%.

Table I provides Carr Index for several common materials.
### Table I: The Carr Index

<table>
<thead>
<tr>
<th>Material</th>
<th>Carr Index (compressibility)</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emcompress (Dical. Phos.)</td>
<td>15</td>
<td>Excellent</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>19</td>
<td>Fair to Passable</td>
</tr>
<tr>
<td>Avicel PH 200</td>
<td>25</td>
<td>Poor</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>31</td>
<td>Poor</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>31</td>
<td>Poor</td>
</tr>
</tbody>
</table>

### Sieving Methods

Sieving plays an important role in the granulation process. The Ro-Tap uses a nested stack of sieves of different mesh sizes, with the largest or coarsest mesh size on top and successively smaller mesh sizes toward the bottom. A cover goes on top and a collecting pan sits on the bottom. Each sieve within a stack should be different from the adjacent by a factor of root 2 or 1.414, e.g., if the coarsest sieve is US 18 mesh (1000 microns), divide 1000 by 1.414 and hence, the next will be 707 microns, in this case 710 microns (closest to 707), which is US 25 mesh.

In the ASTM method, sieving is conducted for 20 minutes, pausing and then sieving again for 10 minutes.

To determine the particle-size distribution, plot data on standard logarithmic paper to compare particle size with the cumulative percentage of undersize particles. The mean particle size (the 50% value) is obtained. If the line is straight then the material has a normal bell-shaped size distribution. If the line is curved then the material has a bimodal distribution—indicating the presence of excessive amounts of fine or coarse particles that were different from the bulk of the material.

### A Decision Tree for the Tablet Process

Before deciding on a tabletting method, the formulator should ask himself several key questions: Is direct compression feasible? Is the blend cohesive? Is there acceptable flow? Acceptable content uniformity? Acceptable bulk density? If the answer is yes to all these questions then direct compression is feasible.

However, if the answer is no to all of these questions, then granulation is the best option. The formulator should also determine whether or not the material is moisture sensitive or if it degrades upon drying. If the answer is yes, then the proper method is dry granulation. If the answer is no, then dry or wet granulation may be necessary.
Of course, over the years, the pharmaceutical industry has developed its own preferred methods of tablet processing. Direct compressions is most favored, followed by wet granulation/fluid bed drying; Wet granulation/tray drying; and roller compaction (dry compression).

Within the wet granulation drying method, generic manufacturers favor tray drying by a ratio of 2:1, whereas innovators prefer fluid bed drying by a ratio of 3:1.

But clearly, direct compression is the method of choice among generic manufacturers, with 43% calling it their first choice. In comparison, just 27% of innovator companies call DC their first choice. Generic companies favor DC since it is the cheapest, while innovator companies favor the wet granulation/fluid bed drying process because of uncertainty over drug properties during scale-up.

Tablet manufacturing using the wet granulation process is a nine-step process that requires the milling of drug and excipients; mixing of the milled powders (or addition of ingredients directly to the granulator); preparation of the binder solution (or the binder is added directly to the granulator); mixing the binder solution (or water/water-alcohol co-solvent) with powder mixer to form wet mass; coarse screening of wet mass using 6- to 12-mesh (not needed in high shear granulators); drying moist granulation; screening of dry granules; mixing screened granules with pre-screened lubricant and tablet compression.

In contrast, direct compression requires just three steps: milling of drugs and excipients, mixing of ingredients and tablet compression.

Dry granulation, on the other hand, calls for six steps: milling of drugs and excipients, mixing of milled powders, compression into large hard tablets called slugs; screening of slugs; mixing of lubricant; and disintegrant and tablet compression.

Dry granulation also requires roller compaction. In this process, the powder is fed into two counter-rotating rolls by either gravity or force-fed screws. Once the powder is drawn into the nip angle area, it rubs against the roll surface and undergoes pre-densification. As the material enters the roll gap, particles are deformed or fragmented to form ribbons. The ribbons are sized through a screen and tablet compression takes place. However, ribbon formation involves several variables including roll speed, roll pressure, horizontal and vertical feed screw speed and roller compactor design. Granule formation variables include milling speed, screen type and mesh size and blade configuration.

Of course, in addition to the tablet making process, formulators also have a preference for the type of excipients they use to formulate tablets. More than a decade ago, Shangraw, et. al., published an article in Pharmaceutical Technology detailing the formulators’ preference for certain fillers/binders. Their responses are shown in Table II. Table III
shows their preference for disintegrating agents. Table IV shows some lubricant levels used in tablet manufacture.

<table>
<thead>
<tr>
<th>Table II: Preferred Fillers/Binders</th>
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</thead>
<tbody>
<tr>
<td>Reason</td>
</tr>
<tr>
<td>Solubility</td>
</tr>
<tr>
<td>Cost</td>
</tr>
<tr>
<td>Compactibility</td>
</tr>
<tr>
<td>Supply</td>
</tr>
<tr>
<td>Handling</td>
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<tr>
<td>Physiological inertness</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table III: Preferred Disintegrating Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason</td>
</tr>
<tr>
<td>Disintegration/Dissol.</td>
</tr>
<tr>
<td>Cost</td>
</tr>
<tr>
<td>Compatibility</td>
</tr>
<tr>
<td>Uniformity of supply</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concentrations-%</th>
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</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table IV: Preferred Lubricant Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient</td>
</tr>
<tr>
<td>Magnesium St.</td>
</tr>
<tr>
<td>Stearic acid</td>
</tr>
<tr>
<td>Hydrogenated veg. oil</td>
</tr>
<tr>
<td>Talc</td>
</tr>
</tbody>
</table>

Of course, when compiling a list of preferred excipients, remember that they should be acceptable worldwide and have Pharmacopeial status (e.g., NF/PhEur/JP or equivalent.
national standard).

Some of these materials include:

**Filler:** Lactose monohydrate, lactose anhydrous, microcrystalline cellulose, calcium phosphate dihydrate, mannitol.

**Binder:** Hydroxypropyl cellulose (added dry or wet), hydroxypropyl methylcellulose (low viscosity grades), povidone, starch pregelatinized.

**Disintegrant:** Sodium starch glycolate (Explotab), croscarmellose (Ac-di-Sol), crospovidone (all 2-5% in dry form), microcrystalline cellulose, starch (5-10%).

**Wetting Agent:** Sodium lauryl sulfate (0.5% or less).

**Lubricant:** Magnesium stearate—must use vegetable derived, stearic acid (0.2-2%)%

**Film Coating Agent:** Hydroxypropyl cellulose, hydroxypropyl methylcellulose (low viscosity grade).

**Antiadherent/Glidant:** Talc (1-5% as AA and 0.2-0.3% as glidant).

**Colorants:** Red/yellow iron oxide, FD&C Blue #2 (and its aluminum lake), D&C yellow #10 and titanium oxide as an opacifier.

**Diluents:** Increase bulk volume to a reasonable size dose size, to assist dose preparation, and to affect the release rate of the drug.

**Calcium Phosphate Dibasic, USP:** Practically insoluble in water/alcohol. It has good flow properties but is abrasive and requires a lubricant for tabletting; incompatible with aspartame, aspirin. The surface of milled particles is alkaline and should not be used with drugs that are sensitive to alkaline pH.

**Calcium Phosphate Dihydrate, Dibasic, USP:** It is nonhygroscopic and loses its water of crystallization below 100°C.

**Cellulose Microcrystalline, NF:** It is partially depolymerized cellulose prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material. It occurs as a fine, white powder consisting of free-fibrous, nonfibrous particles. It is insoluble in water.

**Dextrose Excipient, NF:** It is a sugar usually obtained by hydrolysis of starch that contains one molecule of water of hydration. It is freely soluble in water. It may cause browning in tablets containing amines.
Lactose Anhydrous, NF: It is primarily beta lactose or a mixture of alpha and beta lactose. It is freely soluble in water.

Lactose Monohydrate, NF: A natural disaccharide obtained from milk. It is available in different grades of varying particle size distribution and flow characteristic. It is incompatible with amino acids.

Mannitol, USP: It has a sweet taste and freely soluble in water. It is commonly used in direct-compression tablets and chewable tablets.

Starch, NF: It consists of the granules separated from the mature grain of wheat or tapioca. It is insoluble in cold water and in alcohol.

Starch, Pregelatinized, NF: It is starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. It is directly added as a powder to a premix before incorporating water to granulate. It is slightly soluble to soluble in cold water.

Sugar, Compressible, NF: It may contain starch, malto-dextrin or invert sugar. It contains between 95% and 98% sucrose. It is used in the preparation of direct-compression chewable tablets.

Diluents compress by plastic deformation (microcrystalline cellulose) or brittle fracture (dicalcium phosphate dihydrate). Successful tablet production involves having the right balance between the two properties.

When selecting excipients for DC tablets, it is important to remember that besides possessing good flow and compression properties, these excipients must also possess the following attributes:

• Particle size distributions that are similar for most active drug substances, thus avoiding segregation during processing.

• High bulk density.

• Batch-to-batch quality must be reproducible.

• Materials that act as disintegrating agents with poor flow characteristics—microcrystalline cellulose and directly compressible starch.

• Free-flowing materials that do not disintegrate, such as dibasic calcium phosphate dihydrate.

• Free-flowing materials that disintegrate by dissolution – lactose, mannitol.
Co-processed excipients.

Clearly, the formulator has an array of ingredients and production methods to choose from when developing tablets for pharmaceutical use. But selecting the right combination of excipients and processes is critical to successful tablet making.

References

1. Ref. X. He, Amer. Pharm. Review, p. 26