A tablet with good characteristics is not made on a tablet press; it is made in the granulation process. Joining particles within a given granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity, and reduced down time. The objective of the process is to combine ingredients to produce a quality tablet.

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This article presents the basic technologies for preparing powders for tablet making. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. If one were to make tablets from granulated sugar versus powdered sugar, for example, powdered sugar would be difficult to compress into a tablet and granulated sugar would be easy to compress. Powdered sugar’s small particles have poor flow and compression characteristics. These small particles would have to be compressed very slowly for a long period of time to make a worthwhile tablet. Unless the powdered sugar is granulated, it could not efficiently be made into a tablet that has good tablet characteristics such as uniform content or consistent hardness. The granulation process combines one or more powders and forms a granule that will allow the tableting process to be predictable and will produce quality tablets within the required tablet-press speed range.

A tablet formulation contains several ingredients, and the active ingredient is the most important among them. The remaining ingredients are necessary because a suitable tablet cannot be composed of active ingredients alone. The tablet may require variations such as additional bulk, improved flow, better compressibility, flavoring, improved disintegration characteristics, or enhanced appearance.

If the active ingredient in a formulation represents a very small portion of the overall tablet, then the challenge is to ensure that each tablet has the same amount of active ingredient. Sometimes, blending the ingredients is not enough. The active ingredient may segregate from the other ingredients in the blending process. The ingredients may be incompatible because of particle size, particle density, flow characteristics, compressibility, and moisture content. These incompatibilities can cause problems such as segregation during blending or during transfer of the product to the press as well as separation of the active on the tablet press.

Granulating the active by itself and then blending it with the rest of the ingredients is one solution to the segregation problem. Or, all or most of the ingredients could be granulated together. The best course of action to ensure that each tablet contains the correct amount of active ingredient, especially if the active is only a small percentage of the tablet ingredients, is to mix the active thoroughly with some or most of the other ingredients and then granulate the blend (i.e., form the blend into granules). Each granule would contain a little of each of the ingredients, and the active ingredient would be distributed evenly.
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throughout the blend. The link between particles in each granule must hold the particles together and keep them from breaking apart before they are compressed.

If the active ingredient represents a high overall percentage of the total tablet, then the active must flow, compress, and eject from the tablet press and disintegrate properly. Even in this case, most actives do not cooperate. To solve this problem, the active must be granulated by itself, blended with the other ingredients in the formulation, and compressed on the tablet press. The nature of the active must be understood and its characteristics may have to be improved to make this process work. Some actives are very fine, small particles that are lighter than other particles. Even if the active is the correct size it may not flow smoothly, and flowability is very important to making a good tablet. Furthermore, the active could be the right particle size and it may flow well, but it may not blend well with the other ingredients. The active may be too dry or too moist, which prevents proper compression. Once the challenges to making an active perform well are determined, the objective can be identified and granulation can begin.

This article explains in simple terms the fundamentals of the granulation process. Three basic techniques are used to prepare powders for compression into a tablet: direct compression, wet granulation, and dry granulation. Ten different formulations would probably require that the powders for each of the formulations be prepared in various combinations. This article investigates the three techniques and discusses how to determine which method is best for individual formulations.

Direct compression

Direct compression is used when a group of ingredients can be blended, placed onto a tablet press, and made into a perfect tablet without any of the ingredients having to be changed. Powders that can be blended and compressed are commonly referred to as directly compressible or as direct-blend formulations. Blending the powders, putting them onto a tablet press, and seeing what happens is the most direct way to make a tablet. Sometimes the tablet will fall apart, the active ingredient won’t be in all the tablets (no content uniformity), or all the powders won’t fit into the die cavity (the place where powders are filled on the tablet press). Simply blending powders does not form a granule. When powders do not compress correctly, they must be granulated. Nevertheless, not all products must be granulated. Many processes are unnecessarily implemented because the objective and reason for choosing a process path were incorrect. Before choosing a means to process a formula, the best course of action is to put the product on the press to see what happens.

Excipients

Ingredients in a tablet other than the active ingredient are called excipients. Excipients can help powders become more fluid. This fluid motion is very important for transferring powders into the die cavity for compaction. Many years ago a high-speed tablet press could produce 50 tablets/min. Now a tablet press that runs this slowly is called a laboratory development press, and it is good only for basic feasibility studies. Today’s high-speed tablet presses can produce up to 12,000 tablets/min, and the average tablet press speed is 3000 tablets/min. Therefore, excipients are used not only to enhance the performance of active ingredients, but also to simply make the active work better on the tablet press.

Many types of excipients are used in tablet formulations to help in other ways. They include

- binders, which help powders fuse or link particles to one another
- fillers, which bulk up a tablet
- lubricants, which prevent powders from sticking to the metal components of the tablet press and tablet-press tooling
- disintegrants, which help the tablet break up after it is ingested by the patient

Several other excipients can be added to a formula to improve flow, compression, hardness, taste, and tablet performance.

Flowability

As mentioned previously, press speed requires powders to be very fluid, a property commonly referred to as product flowability. Good flow characteristics are necessary because the mechanical action of the tablet press requires a volume of fill. As shown in Figure 1, the volume of fill represents the actual tablet weight. A tablet press does not weigh the precise amount of powder for each tablet. To achieve consistent tablet weights, the formula must be designed to flow consistently and to fill volumetrically. Thus the powders in the formula must possess a consistent particle-size distribution and density to attain proper flow and achieve volume of fill (i.e., tablet weight). In other words, the powders must flow consistently to attain consistent results.

Compressibility

Other excipients in a formula enhance the ability of the powders to compact. All powders have very different characteristics. Remember your first chemistry class and the sessions during which you began to understand the periodic table? The basic structure of an atom has physical characteristics: shape, density, and structure. Compressing a tablet of many different powders that have varying physical characteristics can be dif-
ficult. Think about the example of making a snowball to throw at your buddy: If the snowflakes are rather large and wet, then they compact very easily into a snowball. However, if the snowflakes are very light, fluffy, and dry, then compaction is more difficult. Every kid knows that to make a snowball with light, fluffy, and dry snowflakes, they must hold the snowball together for a longer period of time (dwell time) and be careful not to overcompress. If the snowball is overcompressed, then the flakes no longer lock together but instead laminate (flatten out) and fall apart. The same is true of powders used in pharmaceutical tablets. If the formula has some of both characteristics—large particles with high moisture content and small, dry particles—then the tablet may or may not compress well and probably will have difficulty holding together. One of the main reasons to granulate powders is to make them more compressible.

Wet granulation

When powders are very fine, fluffy, will not stay blended, or will not compress, then they must be granulated. Fluffy is not a technical term, but it fits the problem well; it means that the required quantity of powder physically will not fit into the die cavity on the tablet press. The volume of fill (bulk density) is greater than that which is mechanically allowed.

Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available.

Some powders require the addition of only small amounts of a liquid solution to form granules. The liquid solution can be either aqueous based or solvent based. Aqueous solutions have the advantage of being safer to deal with than solvents. Although some granulation processes require only water, many actives are not compatible with water. Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together. However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required. Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is not soluble in water, so a solvent must be used to carry the PVP particles in a liquid solution. When PVP and a solvent are mixed with powders, PVP forms a bond with the powders during the process, and the solvent evaporates (dries). Once the solvent has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules.

Many different types of binders exist. Some binders, called wet binders, only work when added as a solution. Dry binders are preprocessed powders that when mixed with other powders help bind the ingredients together. Binders that can be used wet or dry are also available.

Density

The density of each granule is increased by increasing the amount of binding solution as well as the mechanical action of the mixer. Therefore, controlling the amounts of solution, binder, and mechanical action allows one to control the strength and density of the granule. Machines that are used for this process are called granulators. Granulators can be low shear, medium shear, or high shear. Shear is the amount of mechanical force of the granulator. A low-shear granulator uses very little mechanical force to combine powders and binding solution. The fluid-bed granulator, the most commonly used low-shear granulator, uses a high volume of air flow to elevate powders in a chamber while a binding solution is sprayed onto the particles to form a light bond. A fluid-bed granulator does not impart mechanical energy but instead relies on the powder characteristics and the binding solution to form the lightly held powders into granules. A low-shear granulator will not produce a dense granule, and a high-shear granulator will not produce a light granule. Again, the objective must be understood before the granulation equipment is chosen.

Figure 2 shows a Lodge, a high-shear mixer. The high speed of its mechanical sweeps produces a very dense granule. The main objective of a granulator is to produce the correct granule density. One granulator will not work for all powders. Overgranulating or overdensifying powders can produce a very excellent granule, but the granule could be too dense. For example, if the objective is to make an effective headache remedy and the product is overgranulated, then the tablet may take a long time to disintegrate and dissolve into the blood stream. If my headache remedy takes two hours to work, I probably won’t be in business very long.

Traditional wet granulation

Traditional wet granulation, which is still commonly used, is the process of mixing and adding solution and then transferring the product to a tray dryer (see Figure 3). Wet massing is the process of adding a solution to a blended powder and mixing for a predetermined period of time at a given mechanical speed. Once the process is complete, the wet mass is milled, spread on trays,
and dried in a tray dryer. The wet mass usually is passed through a low-shear mill and then dried for 8–24 h. A drying process that is too short will produce granules that have entrapped moisture; if the process is too long, then the granules become very dry and friable. If granules that have been dried only on the outside reach the tablet press, then moisture will escape the granules during compression and cause the granules to stick to the tablet-press tooling, a problem called case hardening.

Air flow and temperature control must be uniform throughout the entire drying chamber of a tray dryer. If the dryer has poor air circulation, then the product on the top trays will become drier than the product on the bottom trays. Overly dry product breaks apart easily and is no longer in a granular state. When an overly dry granulation is milled, it produces fine dry particles commonly referred to as fines. Fines do not flow well on a tablet press and thereby cause weight variations. In addition, fines do not compress well and can contribute to capping and lamination which are common tablet defects.

On the other hand, compressing the lower-tray granulations, which may contain too much moisture, can cause granules to stick to the tablet-press tooling, another situation that produces defective tablets. The error that is most common to granulation processes is the mixing of overdried granules, overwetted granules, and good granules. Once this mixture is on the tablet press, the full range of the previously described problems ensues: capping, lamination, picking, sticking, and tablet weight and hardness variation.

Problems on the tablet press
Measurement and sampling within a tray dryer can reveal potential problems before they reach the tablet press, but problems with granulation may not show up until the product reaches the tablet press. Capping and lamination can be controlled to some extent by making the tablet high in the die and by slowing the machine down and extending dwell time, which gives the granules and powders time to lock together and form a good tablet. If moisture escapes the case-hardened granule, then the product sticks to the punches. This problem is called picking or sticking. The press operator can increase pressure to allow the granules that are stuck to the metal punch tip to restick or adhere to the tooling instead of the tooling. When compressing case-hardened granules, making the tablet softer may help prevent entrapped moisture from reaching the surface of the granule. However, this course of action may result in tablets that are too soft, thereby failing to completely eliminate the problem of granulation sticking in the punch tips. In these circumstances, press operators often remove the punches and polish them.

Polishing the punches with a paste leaves a slight residue that acts as a mold-release agent and halts the sticking for a short period of time. Cleaning the punch tips with isopropyl alcohol, however, hinders mold release, and the sticking problem reappears. Operators must question whether the polishing is truly a better choice than the simple application of a mold-release agent. Many sticky granulations require a few minutes to fine-tune on a tablet press, and once the settings for weight, thickness, and hardness are just right, the sticking will be minimized and may completely disappear.

Stopping the press once the sticking problem is eliminated requires that the start-up cycle on the tablet press begin again, including polishing of the punches (or adding a mold-release agent). This cycle can become endless. An entire industry is focused on punch-polishing equipment and technology, the so-called Band-Aid approach. If punches must be polished during a run, then perhaps the granulation process is incorrect. Blame should not fall to the tablet press, press tooling, polishing, or the press operator; the problem should be corrected in the granulating department.

A common complaint about product development is that an adequate quantity of active ingredients is not available to properly study real granulation problems. Substitutes are sometimes used that do not replicate the active ingredient correctly, making feasibility studies difficult. Once a product is scaled up, the real problems that weren’t fully discovered in development hit the production floor. When the problems are met head on at the production level, the solution often is to polish the punches. In reality, the product may not have been fully developed and may remain a problem while it is in production.

Dry granulation
The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling or on a roller compactor commonly referred to as a chilsonator (see Figure 4). When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in
Roller-compaction or dry-granulation equipment offers a wide range of pressures and roll types to attain proper densification. This equipment is loud and dusty compared with other process machinery. Material feed rates are critical for attaining the final objective. The process may require repeated compaction steps to attain the proper granular end point. Typically, a percentage of product does not get compacted and may require screening to remove excessive fines. Again, successful compaction depends on the compatibility of the products being compressed. If fines are not removed or reprocessed, then the batch may contain too many of them, a situation that can contribute to capping, laminating, weight, and hardness problems on the tablet press. The need for screening large amounts of fines is common to roller compaction, and the degree to which it can be managed depends on the nature of the ingredients. Any product that is removed from the rest of the batch because of particle size must be analyzed to determine what is being removed. Roller compacting the complete formula is not usually necessary. The object is to densify powders and form granules of the products in the formula that must be compacted, mill the granules, and then blend them back in with the rest of the formula’s ingredients. Most dry-granulated products do not have problems with picking and sticking because moisture is not present.

Summary
In the pharmaceutical industry, most products are manufactured using the wet granulation process. Wet granulation offers a wide range of capabilities for forming granules, from the production of light granules to the production of very dense granules. More than 70% of the global industry’s granulations are made using this method.

Directly compressible materials are preprocessed or are found naturally in the granular state. Ingredients that are preprocessed are subject to some variation in particle-size distribution and density variation, leaving the user subject to the quality of the supplier’s product. The reduced number of processing steps required by directly compressible materials allows for less equipment and shorter process times in comparison with wet- or dry-granulation processes.

When products are dry granulated, the process times are often reduced and equipment requirements are streamlined; therefore, the cost is reduced. However, dry granulation often produces a higher percentage of fines or noncompacted products, which can lead to compromised tablet quality or yield problems if the product is not compacted correctly.

Pharmaceutical products are processed all over the world using the direct-compressing, wet-granulation, or dry-granulation methods. Which method is chosen depends on the ingredients’ individual characteristics and ability to properly flow, compress, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied.