granulation

Recent advances in granulation theory, modeling, and process control

Dilip M. Parikh
DPharma Group

A better understanding of granule formation mechanisms, modeling, and process control is turning the "art" of granulation into a science. This article provides an overview of these advances, highlights the research underlying them, and discusses how they are transforming the granulation process. The article focuses on the batch processes most widely used in pharmaceutical operations.

Granulation is an important unit operation in the pharmaceutical industry, and over the last 25 years we've seen many advances in our understanding of the process. This new knowledge is helping process engineers and others to design efficient commercial manufacturing operations and, in some cases, is prompting a shift from batch processing to continuous roll compaction, melt granulation, and spray drying. This article describes the research that is advancing our understanding of granule growth, process modeling, process control, and other key aspects of the process.

The role of granulation

The main objectives of granulation are to improve the flow characteristics of a powder mixture, decrease dustiness, and prevent components of the mixture from segregating. In short, granulation is particle design, and the properties that the particles acquire after granulation depend on their size and on the physico-chemical properties of the drug substance and binder. Making a granule that has the intended attributes requires controlling the formulation components and the process.

There are two major types of granulation methods: wet and dry.

Dry granulation methods

The primary advantages of dry granulation are its simplicity and low cost. There are three common methods.

Direct compression. This method simply combines the drug-substance powder with the excipient powders in a blender. The blend then moves directly to a tablet press or capsule filling machine.

Slugging. In this method, poor-flowing blends are compressed using a rotary tablet press fitted with a die much larger than the die used to make the final tablet, forming "slugs." Slugs are typically 1 inch in diameter or larger, and there is little attention paid to weight variation or compression properties. Instead, the objective is to make the slug as hard as possible. Next, the slugs pass through a mill, join additional excipients in a blender, and are transferred to a tablet press or capsule filling machine. Occasionally, products require double slugging to densify the mixture enough to obtain the desired flow properties.

Roller compaction. In this method, typically used with moisture-sensitive drug substances and formulations with poor flow characteristics, the material flows between two rollers that compact it. The rollers come in a variety of designs so the formulator can produce compacts of the correct hardness. The compacts are subsequently milled, blended, and made into tablets or filled into capsules. In addition to its ability to process poor-flowing and moisture-sensitive materials, roller compaction entails low labor costs and can be adapted for continuous production.

Wet granulation methods

Wet granulation methods introduce a fluid onto a shearing mass of fine powders contained in a vessel. Wet granulation equipment includes low-shear and high-shear mixers, fluid-bed processors, rotating drums, and pan mixers. Successfully agglomerating primary particles requires controlling the adhesional forces between particles. It's these forces that encourage agglomerates to form and grow and that determine whether the agglomerates have sufficient mechanical strength. The rheology of the particles before they're agglomerated is sometimes also critical to rearranging them in a way that permits densification of the agglomerate and development of an agglomerate structure that suits end-use requirements.

Advances in granulation theory

Many researchers have used empirical methods to study how the material properties of the granulating powder and how the process conditions influence the granulation process. Recent studies, however, emphasize the influence of material properties and the particle wetting mechanism. Iveson et al. presented an excellent review of the wet granulation process [1]. Other researchers have added to our understanding of the traditional granulation process [2] and proposed a more modern approach [3].

Iveson and his co-authors advanced the understanding of the granulation process by identifying three fundamental sets of rate processes within the granulation process that are important in determining wet granulation behavior:

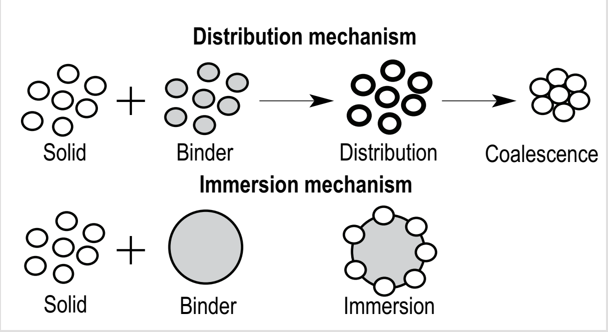
1. Wetting and nucleation
2. Consolidation and growth
3. Breakage and attrition

According to this view, understanding these processes enables you to predict how formulation properties, equipment type, and operating conditions affect granulation behavior, so long as you can adequately characterize them. Iveson and co-authors also cited other work that describes the current thinking about granule growth [4, 5, 6, 7].

In the wetting and nucleation stage, the powder is strongly influenced by the spray rate or distribution of the binding fluid and by the properties of the powders. In the consolidation and growth stage, partially wetted particles and large nuclei coalesce to form granules and develop internal voidage, also known as granule porosity. In the breakage and attrition stage, the granules that are inherently weak or that developed flaws during drying are particularly susceptible to attrition. Schaefer and Mathiesen proposed two different mechanisms that cause nucleation in a high-shear mixer: distribution and immersion [8]. See Figure 1.

FIGURE 1

Nuclei formation mechanisms (adapted from Schaefer and Mathiesen [8])



Distribution mechanism. This occurs in cases where the binder droplets are small. They coat the primary particles, and the wetted particles coalesce to form initial granules. Low-viscosity binders and high-speed impellers promote the occurrence of this mechanism.

Immersion mechanism. This occurs when binder droplets engulf the primary particles. It commonly occurs when binder viscosity is high and impeller speed is low.

Ennis proposed a model to describe the influence of viscosity on granule growth when wet-surface granules coalesce [9]. In this model, when two granules collide, a viscous liquid layer surrounding the granules dissipates the impact energy. If the impact energy is high and the viscous liquid layer cannot dissipate all the energy, the granule rebounds instead of adhering. If all the energy is absorbed, however, the granules stick together. This explains why granules formed in a high-shear mixer are denser than those formed in a fluid-bed granulator: The granules deform during processing in proportion to the intensity of bed agitation. Where large granule deformation occurs during granule collisions, granule growth and consolidation follows [10]. See Figure 2. Rather than "sticking" together as often occurs in the low-deformability environment of fluid beds, high-shear mixers "smash" the granules together. In short, high-agitation, high-deformation processes generally produce denser granules than low-agitation, low-deformation processes.

The breakage mechanism is strongly influenced by material properties and bond strength, and any granule breakage mechanism that causes a continuous exchange of primary particles promotes granule homogeneity. Breakage in a high-shear mixer is of significant importance. There are various forms of breakage, including cleavage of particles and particle-surface attrition, in which granules are chipped when they collide with other particles, vessel walls, or the impeller.

Granulation process modeling

Granulation, like most other solids processing operations, is still not well understood. But there are a variety of tools available to increase understanding and to provide an integrated systems approach to measuring, analyzing, optimizing, controlling, and modeling the granulation process. In its draft guidance for industry [11], the FDA categorized these tools:

1. Multi-variate data acquisition and analysis tools
2. Modern process analyzers or process analytical chemistry tools
3. Process monitoring, control, and end-point identification tools

Granulation modeling is an area of growing importance, and particle size distribution of the granules has primary importance because it relates directly to product quality. There are a variety of techniques to investigate, model, and control the evolution of granule size distributions. There are also several approaches to modeling process systems. At one end is mechanistic modeling, which seeks to apply fundamental physics and chemistry. At the other end is empirical modeling, which tries to fit an arbitrary function into the input-output data. Cameron and Wang provide an excellent review of granulation modeling [12].

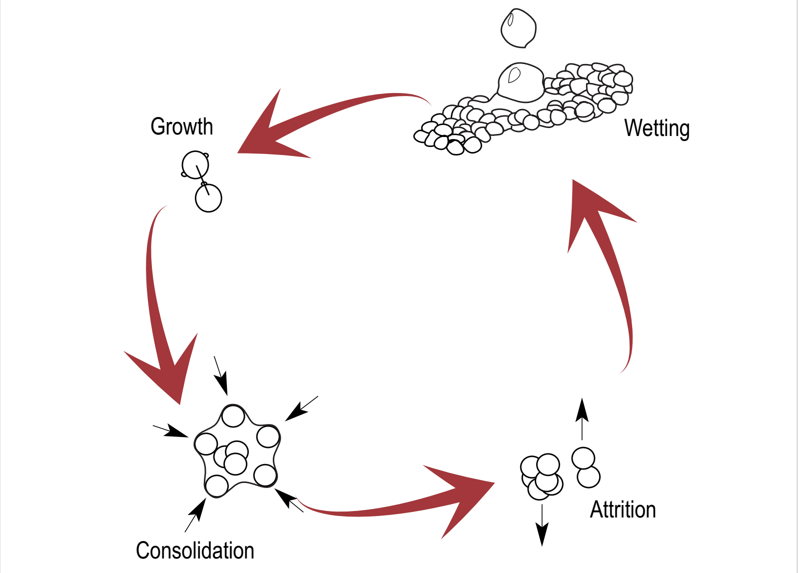
Mechanistic modeling. This approach uses the principles of mass, energy, momentum, and population balances to track particle size distributions as various particulate phenomena take place. This type of modeling is very time consuming and costly compared to empirical modeling.

Empirical modeling. This approach is based on actual plant data and is used when the granulation process has not yet been selected. Typically, input-output data is gathered at fixed intervals, and the structural form of the model and the parameter values normally have no physical significance. The application of empirical modeling is limited, and extrapolation of data is not advisable.

Multi-variate analysis. Multi-variate analysis deals with data that contains measurements of more than one variable for a number of objects. It searches for interdependence among all the process variables identified during development. Multi-variate methods use latent variables, which are linear combinations of the original variables. Latent variables in the data are directions that cannot be measured directly, but

FIGURE 2

The rate processes of agitative granulation, which include powder wetting, granule growth and consolidation, and granule attrition, combine to control granule size and porosity. These rate processes may be influenced by changes to the formulation or the granulation process (adapted from Ennis [10]).



are principle properties that explain most of the variation between the objects.

Also known as statistical modeling or statistical analysis, it's an approach that describes the granulation process using experimental results instead of theories based on fundamental principles. Models must be based on a clear understanding of the process from a systems-engineering standpoint. In the granulation process of a pharmaceutical product, for example, the "difficult-to-measure" variables are the settings of the process variables, the properties of the produced granules, and the subsequent dosage forms. These parameters are hard to measure because there is very little of the new product available for conducting a series of experiments.

Artificial neural network. An artificial neural network (ANN) predicts events or information based on learned pattern recognition. An ANN is a computer system that mimics the operations of the human brain by mathematically modeling its neural-physiological structure (its nerve cells and the network of interconnections between them). In an ANN, computational units called "neurons" replace the nerve cells, and the strengths of the interconnections are called "weights."

Scientists use ANNs as an alternative to statistical analysis to optimize formulations because they are simple to use and can provide detailed information. An ANN builds a model of the data space that allows you to ask, "What if?" In this way, it simulates some of the ability of the brain, such as learning and drawing conclusions from experience. Using the process control system, quality assurance results, or energy use data, an ANN develops supervisory set points. There are several software products available on the market that deal with these methodologies. However, in order to apply ANN models to online monitoring, many researchers develop specialized, in-house software.

Population balance equation. Particulate solids are characterized by a number of properties, such as size, shape, liquid and gas content, porosity, composition, and age. Size is one of the primary characteristics, but because no two particles are exactly the same size, material is characterized by particle size distribution. In cases where size is insufficient to characterize the particulate system, multi-variate distribution functions are developed. These distribution functions can be predicted through numerical simulations using a population balance equation (PBE). It is a widely used tool in engineering, with applications in crystallization, pharmaceutical manufacture, and related operations [13].

The PBE is much like mass and energy balance equations, except here the balance represents the number of particles of a given size. Particles of a given size may break, decreasing their number (population). Particles may also aggregate with other particles, which also changes the population of a given particle size. Whenever you study the interaction of a large number of particles, you must solve the PBE to determine the properties of the resulting product and its dependence on rate processes (coalescence, breakage, and surface growth). This applies whether they are gas-phase nano-particles, liquid droplets in liquid-liquid dispersions, or solid powder agglomerates.

Models based on PBEs are crucial in the field of particulate process analysis because they allow us to calculate size distribution and to identify the controlling granulation mechanisms. PBEs are particularly useful in process control when used with sensitivity analysis because they enable you to determine how changes to input conditions affect product quality. Pouw et al. proposed a multi-dimensional PBE that uses volume as the intrinsic parameter [14]. This volume-based model tracks the evolution of the volume of solids, volume of liquid, and volume of air of a nucleated granule at each time step.

In 2005, Ndamba et al. presented a paper investigating the effects of relative humidity and temperature on adhesion and granulation of powder particles [15]. They developed a model to predict the optimal end point of wet granulation based on the powder's rheological properties. The model takes into consideration several material properties, including particle surface morphology, contact area deformation, and force applied.

Solving a PBE can be a formidable task. In a mathematical model of wet granulation, Rajniak et al. concluded that combining (a) population balancing of growth and breakage of different granules, (b) a hydrodynamic model of the gas-solid mixture flow, (c) a calculation of physically based coalescence mechanism based on the kinetic theory of granular flow, and (d) a meso-scale model of granule formation offers a promising tool for analyzing and designing high-shear or fluid-bed granulation processes [16].

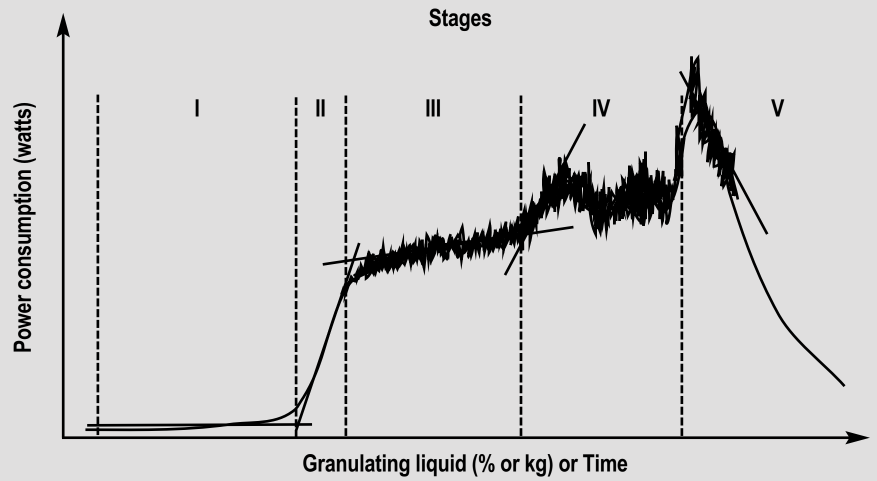
Other recent approaches. In an abstract submitted by Stepanek et al., the authors discussed modeling multi-component granule formation in a wet granulation process [17]. They focused specifically on the problem of finding the relationship between granule composition (porosity, binder-solids ratio, and drug substance-excipient ratio) and the probability of coalescence between two granules of different composition or between a granule and primary particle. They evaluated the probability of wet contact over a statistically large number of simulated collisions using computational experiments and found that the probability was a non-linear function of the functional surface coverage. The obtained dependence of coalescence probability on granule composition was then supplied as an input to a multi-dimensional PBE to predict the composition distribution across size classes. They then compared the result with experimental data from a pilot-scale fluid-bed granulator.

Iveson described a mathematical model for granule coalescence during granulation [18]. His report noted that current models had one of two limitations: Either they considered only whether a bond that formed on impact is strong enough to survive subsequent impacts or they failed to consider the possibility that the bond would rupture after formation. His model accounts for both the effects of bond strengthening with time and for the distribution of impact forces within the granulator. However, his model requires data on the rate at which granule bonds strengthen and data on the distribution of impact forces within a granulator, but neither of these data sets exists at the moment.

Ceylan et al. proposed a theoretical model to describe the system characteristics that affect particle size distribution during granulation [19]. They found that the drop size of the binder liquid had an effect on the degree of granulation achieved, as did powder particle size, residence time, and operating conditions.

FIGURE 3

A typical power-consumption profile obtained from a high-shear granulator (adapted from Leuenberger [29])



Process control of granulation

In the traditional approach to pharmaceutical manufacturing, developers vary the operating ranges of critical process parameters (processing time, temperature, moisture, equipment-specific operating parameters, etc.), and critical quality attributes are measured in the finished product through sampling and laboratory analysis.

But a more suitable system would entail measuring product quality attributes in real time and adjusting the process parameters in response to changes observed in the product. Indeed, increasing automation is central to optimizing production. To develop a functional automation system, however, we need new measuring techniques and new in-line measuring devices.

Solid-water (solid-solvent) interactions are one of the fundamental issues in the pharmaceutical industry. The state of water or solvent in solid material can be characterized using X-ray diffraction, microscopic methods, thermal analysis, vibrational spectroscopy, and nuclear magnetic resonance spectroscopy [20]. Using process analytical technology (PAT) during process development enables researchers to determine critical process parameters and their acceptable ranges. Multiple sensing technologies can be applied so that they simultaneously collect data on the process during development. By examining this data using multi-variate techniques, we can identify critical interactions. In fact, this large amount of real-time data, if properly processed, should increase process understanding. As a result, our ability to model and predict process events should lead to better process reliability and less risk.

What follows is a summary of process control approaches and the current research related to the most common batch granulation processes, including roller compaction and high-shear and fluid-bed granulation.

Process control in roller compaction. Miller investigated near-infrared (NIR) spectroscopy in the static mode to map roller compaction unit operations [21]. Researchers at Purdue University evaluated roller compaction using NIR in the dynamic mode [22]. The team monitored variations in compacted ribbon strength and how the variations could adversely affect particle size and the size distribution of granules obtained after milling compacted ribbons. Other researchers also showed how NIR was useful for monitoring roller compaction [23].

Process control in high-shear granulation. The granule properties of a given formulation are a function of the process parameters, such as impeller speed, amount of granulating fluid, and process time. Determining the end point of a granulation process is critical, and several companies offer methods to predict it using either indirect or direct methods. The photo on page 36 shows a bottom-driven high-shear granulator.

With indirect measurements, sensors monitor the electrical and mechanical parameters of the granulator's motor. This approach is based on the idea that these parameters relate to changes in the consistency of the mixture in the wet granulation process. Power consumption, for instance, has been linked to the level of liquid saturation of the moist agglomerates [24], densification of the wet mass [25, 26, 27], and granule growth [28]. Leunberger proposed that the amount of liquid required for granulation corresponds to the plateau in the power consumption profile [29]. Figure 3 shows a typical power-consumption profile.

The drawback to using power consumption as an indicator is that the signal is affected by a number of factors, such as the formulation, the equipment, and other process variables. Furthermore, power consumption monitoring relies on both the motor's current draw and the voltage. Since high-shear granulators use induction motors that use AC electricity, the current lags behind voltage. An alternative is to measure the motor's torque.

Direct measurements rely on probes, such as the Disona-Boots probe, which was one of the first to market. It monitored the consistency, or strength, of the wet mass, and the value of its results depended on the specifics of the product, so it's rarely used today. Acoustic emission monitoring is a more recent development. This method detects and analyzes the sound produced in the process vessel to determine the end point by correlating changes in the physical properties of the powder mixture with an acoustic emission signal. The technique is non-invasive, sensitive, and relatively inexpensive.

Yet another method monitors the granulation process according to the particle size of the granules. Developed by Watano et al., the system uses an image-processing system connected to a probe that comprises a CCD camera, a lighting unit, and an air purge [30, 31]. In tests, the researchers used the system to measure granule size and product yield of various size ranges during high-shear granulation. These on-line measurements compared favorably with off-line sieve analysis of the granules. Talu et al. took a different approach, using a method that resembled torque measurements [32]. But instead of using average stresses as the information input, they used stress fluctuations.

Process control in fluid-bed granulation. Traditionally, controlling fluid-bed granulation relied on indirect measurements, typically applying the properties of process air as described by Schaefer and Worts [33]. This is an example of monitoring process parameters, but several direct approaches have been developed to measure product parameters (i.e., moisture) and to determine the end point and consequently the in-process particle size. The most promising approach, however, appears to be NIR spectroscopy, which has been widely used to measure water in a variety of applications [34].

NIR can be applied to both quantitative analysis of water and to determining the state of water in solid material. Thus it's a tool for understanding the physico-chemical phenomena during manufacture of the granulation. Usually, for a solid sample, reflected light is the parameter that NIR spectroscopy measures. The incident beam of light is divided into two parts, the transmitted light and reflected light. The reflected light generally consists of two components, the specular and the diffuse. The specular, or mirror-like, component occurs at the interface and it contains only a little information about the chemical composition of the sample. That's why NIR spectroscopy relies more on the diffused component of the reflected light, which is sensitive to particle size and shape distributions, bulk density, surface characteristics, and temperature [35, 36].

Frake et al. demonstrated how NIR performed in-line analysis of moisture content in pellets 0.05 to 0.07 millimeter in diameter during spray granulation in a fluid-bed processor [37]. Rantanen et al. described a similar approach for measuring moisture content using a rationing of three or four selected wavelengths [38, 39]. He and his co-authors reported that the critical part of in-line process monitoring was keeping the probe properly positioned and blowing heated air continuously over the sight glass.

They also reported that wetting and particle growth change the reflection and refraction properties of the granules in a complex manner, depending not only on the wavelength, but also on the absorption properties of the powder matrix and the binder type. Calibration of in-line NIR moisture measurements, even with the fixed-wavelength setup, therefore requires understanding and consideration of the factors affecting NIR signals.

See Vazquez for a comprehensive review of applying Fourier Transform (FT)-NIR to measure fluid-bed drying end points [40]. (FT-NIR is fast and the instruments are easy to use. Measurement accuracy is the same as that of NIR.)

Rantanen et al. used NIR to monitor moisture and airflow [41, 42]. Using an in-line multi-channel NIR multivariate process, they collected data and analyzed it using principal component analysis (PCA). The authors showed that a robust process control and measurement system, combined with reliable historical data storage, could be used to analyze the fluid-bed granulation process. PCA modeling proved to be a promising tool to handle the multi-dimensional data collected and to reduce the dimensionality of the process data. FT-NIR spectra gave information useful for understanding the granule growth and simultaneous drying phenomenon during granulation. The authors used NIR to study moisture measurement combined with temperature and humidity measurements. They also investigated the effect of particle size, particle composition, and binder type on NIR moisture monitoring using a full-range off-line FT-NIR spectrometer [43]. The study revealed that wetting and particle growth changed the reflection and refraction properties of the granules in a complex manner that depended not only on the wavelength, but also on the absorption properties of the powder matrix and binder type.

The non-invasive and multi-variate character of NIR techniques provides an interesting platform for pharmaceutical process monitoring. Reich provides an excellent review of NIR spectroscopy [44].

Additional methods of process control

What follows is a summary of process control methods with the potential for application in a variety of granulation processes.

Self-organizing maps. On-line process data is usually multi-dimensional and is difficult to study with traditional trend and scatter plots. Rantanen et al. suggested using a new tool, called a self-organizing map (SOM), to reduce data dimensionality and to monitor the state of the process [45]. As a batch process, granulation traverses through a number of process states, and an SOM visualizes these as a two-dimensional map. An SOM also enables researchers to study the differences between granulation batches.

At-line measurement. Laitinen et al. presented a paper on using an at-line optical technique to study particle size

[46]. Using a CCD camera with optics and illumination units and with stabilized collimated light beams, the authors took two images of 36 granule samples, alternately illuminating the samples. Two digital images with matrices of their gray scale values were obtained and the differences between the two matrices were calculated. This method provided very rapid (1 minute per sample) measurement of particle size with a very small sample size (less than 0.5 gram).

Focused-beam reflectance measurement. This method uses a focused beam of laser light that scans, in a circular path, across a particle or particle structure passing a window. The particle scatters the light in all directions, and the light scattered toward the probe is used to measure the chord length or the length between any two points on a particle. Devices using this method are available commercially and the suppliers claim they can provide online monitoring and measurement of particle sizes in fluid-bed granulation processes.

Artificial neural network. In addition to its role in process modeling, an ANN can be combined with a process control system to form a product control system. Product control occurs when a system measures defined product attributes in real time and uses the information to adjust the control system. While the process control system runs the process (fans, motors, heaters, etc.), the ANN controls the product (moisture, consistency, etc.). A process control system for a fluidized-bed processor would include an operator interface, sensing elements, and final control elements such as process airflow, temperature, and inlet air dewpoint. The inputs in that case would be inlet air temperature, outlet air temperature, airflow rate, and energy consumption. Additional contributing factors would be the fouling coefficient of the dryer filter bags, quantity of product in the processor, and the type of product and its unique characteristics.

Watano et al. described a practical method for controlling moisture during fluid-bed granulation using an ANN [47]. They wet-granulated a pharmaceutical powder using an agitation-type fluidized bed, and continuously measured moisture content with an infrared moisture sensor. They also developed an ANN for moisture control that used moisture content and its changing rate as input variables. They then used the ANN to investigate moisture control characteristics based on back-propagation learning. Adopting the developed system produced good response and stability without overshoot. The system also maintained its stability under various operating conditions.

Effusivity. One PAT tool is thermal effusivity, the property that dictates the interfacial temperature when two semi-infinite bodies meet. It's sometimes called thermal inertia. It is present in all materials and all formats: solid, liquid, powder, and gas. Effusivity combines thermal conductivity, density, and heat capacity into one value. Effusivity sensors work in the same way your hand differentiates between materials based on touch. The non-destructive, interfacial, and rapid testing capabilities of this sensor make it an ideal online monitoring tool for many processes. Effusivity can be measured directly. One method involves an interfacial device that places a sensor in direct contact with the sample to measure heat flow. The rate of heat transfer from the instrument's heating element is function of the thermal effusivity of the sample material. Wet material, for example, absorbs more heat than dry material. Thus, this multi-variate approach to examining the properties of a material is a function of density, particle size, particle size distribution, lubricant level, morphology, composition and moisture content. Because effusivity measurements take only a few seconds, operators can employ online monitoring to get real-time feedback on the status of the process. Effusivity is used in powder blending operations and is finding application in wet granulation processes as well.

Using interfacial reflectance to measure thermal properties, effusivity sensors rapidly detect consistency, uniformity, and homogeneity of a broad range of materials, from solids and powders to liquids and pastes. Figure 4 shows one company's effusivity sensor, which uses a modified "hot-wire" technique. This means that the sensor supplies the heat (approximately 2° to 3°C) and uses the same metallic filament to measure heat reflected back by the sample. As a result, testing is completed in a matter of seconds and does not damage or affect the sample.

Summary

Our understanding of the granulation processes used to manufacture pharmaceutical dosage forms has increased over the last 25 years because we have increased our basic theoretical understanding of particle wetting, granule formation, granule breakage, and agglomeration mechanisms. This understanding has provided researchers the basis to model the granulation process.

This progress offers us PAT tools to monitor and control processes. In fact, it has become easier to control granulation processes, whether the process involves roller compactors, high-shear mixers, or fluid-bed processors. Each can be subjected to one or more of the new tools or techniques, such as NIR, ANN, power and torque measurements, and effusivity. These are in addition to traditional process controls for temperature, airflow, and moisture. As the technologies and their application becomes more user-friendly, other granulation techniques can be enhanced with these tools.

There is more work to be done to address the variations in powder characteristics and process equipment and the difficulties of scale-up. But research continues in these areas, and that work will lead to robust process development that will enable researchers to scale up predictably. In fact, today's efforts may be a prelude to routine implementation of continuous granulation processes in the pharmaceutical industry. *T&C*

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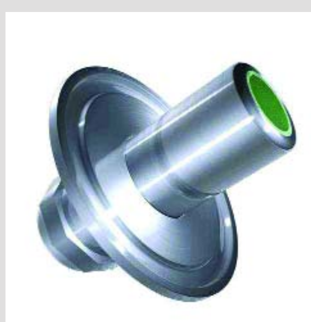
Figure 4

A sensor for measuring effusivity



Courtesy of Mathis Instruments, Fredericton, NB, Canada

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Dilip M. Parikh is president of DPharma Group, a pharmaceutical technology consulting group, 10309 Kingsbridge Road, Ellicott City, MD 21042. Tel. 410 900 8489. E-mail: dpharma@gmail.com. He is an industrial pharmacist by training and has more than 30 years of industry experience at major pharmaceutical companies in research and development, cGMP-compliant facility planning and construction, and manufacturing and operational management. He is editor of Handbook of Pharmaceutical Granulation Technology*, second edition, published in 2005. He is also the author of numerous scientific publications and has been invited as speaker at scientific conferences worldwide.*