

Advances in pharmaceutical materials and processing

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Advances in pharmaceutical materials and processing require new generations of pharmaceutical technologies, which in turn require an improved understanding of each step in the unit processes of dosage form development. The unit processes range from raw material qualification to final product release using process monitoring of critical steps. The authors illustrate some recent research trends in understanding and improving pharmaceutical materials and processing through the use of experience obtained within several research programs at Purdue University (West Lafayette, IN, USA).

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▼ In common with other industries, the pharmaceutical community is preparing itself for advancing into the year 2000 and beyond. Many innovations are taking place, both in the development of new drug delivery systems and the project plans for new drug development activities. All of these areas are important factors in the future of new drug products in any attempt to relieve current or future ailments.

Next generation of pharmaceutical technologies

As technology progresses, pharmaceutical scientists must also move forward to develop improved treatments for both old and new afflictions. An area of particular importance is drug delivery. One of the current activities taking place in this area is site selection for drug absorption in the gastrointestinal tract; possible sites may include the buccal cavity, stomach, small and large intestine and the rectum. Traditionally, drug delivery has been achieved through the small intestinal route, but now other areas of the body are being explored. This movement into advancing drug delivery will impact upon methods used in the

preparation and control of dosage forms, and thus new methodologies may be required for the development of the dosage forms of the future.

Compliance issues

In addition to these considerations are those that involve the US Food and Drug Administration (FDA) and its expectations regarding the documentation of new drug development activities. The agency's interest in the basic formulation development and technology transfer issues has increased during its pre-approval and post-approval inspections. These considerations are important in the design of both the processes and equipment of the future. Pharmaceutical scientists must consider what the agency may require in these areas. It is important to be aware of the fact that FDA pays a great deal of attention to vendor sites and laboratories that may be listed in a new product approval document. At present, a great deal of emphasis is placed on current good manufacturing practices (cGMPs) and how they are committed to new drug applications (NDAs) and abbreviated new drug applications (ANDAs). In terms of clinical trials, documentation and records are important factors in the support of a new product's research and development (R&D), scale-up and commercial production.

Analysis of unit operations

Because unit operations may have to be modified to suit the requirements of a new dosage form, developers' activities in scale-up and production will be carefully scrutinized and thus they must be aware of their processing and equipment needs. As demonstrated in Table 1, the origins of the activity centers around raw material qualification and continuous efforts to improve specifications, which are often beyond those used in

Table 1. Current considerations important to future development of the unit operations for pharmaceuticals

Unit operation/activity	Current status	Next level	Cutting edge
Raw material qualification	US Pharmaceutical specification and methods Internal process specific specification	Improved internal specification including more physical parameters (e.g. shape, surface roughness)	Predictive methods to correlate physical properties to observed behavior (e.g. crystal morphology, fractal analysis of surface roughness)
Drying of hydrates/solvates	Trial and error determination of drying cycle	Full solid-state characterization of components during cycle	Control of forms during drying
Mixing/blending	Variety of blender types monitoring by thief sampling	Bin or high shear blenders Remote monitoring for endpoint determination	Feedback control of process by monitoring device
Dry granulation	High shear blending/slugging	Roller compaction Uniformity monitoring	Full process control through optimization
Wet granulation	High shear and fluid bed granulators (endpoint determination by predetermined time and/or periodic sampling)	Vacuum granulator/dryer combinations (e.g. Zanchetta) Extrusion/sphearization Remote monitoring of granulation endpoint	Control of granule characteristics by real time modification of process
Drying	Tray, fluid bed drying	Standard sampling and testing for water	Near infrared methods
Compression	Rotary tablet presses Compression force or thickness priority	Fully instrumented presses	Feedback-controlled presses
Lyophilization	Empirically determined cycles	Cycle optimization using advanced analytical techniques	'Smart' freeze dryer
End-product testing Packaging	Dissolution, hardness Semi-automated lines Spot inspection	Sampling 100% inspection	Final release by near infrared
Process control	Minimum sampling	Computer data processing improvement	Parametric release
Product containment	Limited equipment	Improvement in container design	Islands of operation

the United States Pharmacopeia (USP). Specifications should become dynamic, and factors such as particle shape or surface roughness have to be considered in attempts to improve the processing of a particular material. It is important to note that product formulation involves the bringing together of particles of different surface morphology and this may impact upon any further processing. In the preparation of various dosage forms, and solids in particular, there are always concerns with the blending of dissimilar materials. These concerns involve not only the blender type, but also the fundamental operational characteristics of the blending device. It is therefore necessary to look to the future for systems that may be able to offer a form of feedback control of the blending process and this will require appropriate monitoring of the system.

One unit operation that is considered more frequently is the preparation of granules for tableting. These are prepared by

either dry granulation techniques (using roller compaction) or wet granulation. Problems associated with wet granulation may make it necessary to adopt the dry granulation technique in order to achieve adequate control of the distribution of the active ingredients. Advances have been made over the last ten years, although there is often inadequate control over the granule characteristics, and there is a need to optimize the process of wet granule formation. This will require certain modifications of the process, or a second look at methodologies that have been discarded. The monitoring of the endpoint of wet granulation is still a technique of concern and various methods of monitoring the endpoint of wetting require examination. There is interest in the general monitoring of drying, optimization of tablet machines in current use, and investigations into freeze-drying techniques for improved or optimal product preparation methods.

In-line and on-line control

In an analysis of the various pharmaceutical unit operations, it is possible to identify some in-process control parameters that can be monitored so that the collected data can be fed into a computer. This will allow release of the product by so-called 'parametric' procedures. Parametric release presents a challenge to those involved in solid dosage forms because of the limited amount of techniques currently available for in-process monitoring.

Of current concern is the need for containment, which is necessary for worker protection when the active drug is a highly potent material. Containment allows the manufacturer to transfer materials during various manufacturing steps, including in-process manipulation of materials and then final transport to a tablet machine area or a capsule filling area without production personnel contact. The manufacturing plant of the future will contain isolated areas, which are sometimes referred to as 'islands of automation'. These are sub-units within a process design for the purposes of containment. Certain types of drug substance may frequently require manufacturers to be completely enclosed in appropriate suits with connecting air supplies, and thus it may be possible to work within these islands of automation and eliminate risk of worker exposure to hazardous substances. The authors have experience with 'lights out' operation, and within tablet manufacture in particular. This method is a further design element that would require decreased levels of personnel contact with the material. The pharmaceutical processing plants of the future will need to have rigorous containment capabilities.

Purdue University has been recognizing the need to improve both pharmaceutical processing and the characterization of pharmaceutical materials. As part of these efforts, Purdue University has established the National Science Foundation (NSF) Industry/University Cooperative Research Center in Pharmaceutical Processing, and, with the Massachusetts Institute of Technology (MIT), the Consortium for Advanced Manufacturing of Pharmaceuticals (CAMP). Through the NSF Center and CAMP, faculty members associated with the programs are involved in cutting edge research in pharmaceutical materials and processing. This article describes several projects at Purdue University that are supported by the two programs. In specific terms, strategies for the identification and control of processing variables in each unit operation of the pharmaceutical manufacturing process are described. There are other promising approaches under development which are not addressed here.

Physical properties in raw material qualification

Raw material qualification is an important part of process validation and it is becoming increasingly important as economic reasons lead to an increase in levels of outsourcing of the manufacture of active compounds. Variation in raw materials

Box 1. Issues in qualification of physical properties

- Lot-to-lot and batch-to-batch variation
- Variation in material from alternate supplier
- Representative sampling establishing meaningful specification
- Scaling results
- Appropriate characterization methods

can lead to failures in production and/or dosage form performance, which are often attributed to an uncontrolled process. Conversely, a process is not in control if it is not 'rugged' enough to be able to accommodate the normal range in variation of the physico-chemical properties of its components. Some of the major issues surrounding physical property qualification are listed in Box 1.

Lot-to-lot and batch-to-batch variation occurs because the raw material supplied by either an internal or external source is also the result of a process with its own intrinsic variations. The limits of variation should be defined for a controlled process; however, suppliers cannot be expected to control those properties that are of differing levels of importance to each manufacturer. Since multiple suppliers of a component are typically identified in the NDA, ANDA or supplementary new drug application (SNDA) stage, the variation in materials received from different suppliers must be examined carefully. A major problem is representative sampling; that is, in attempting to obtain analytical results on a small sample that represents the true characteristics of the bulk product. In terms of difficulty, this is second only to trying to obtain a representative sub-sample. The results of lab- and/or pilot-scale testing can have a variable relationship to behavior at levels at the production scale. Therefore, the range of acceptable variation must be carefully established prior to technology transfer. It may be necessary to stress the limits by producing batches of product with the selected raw material that are at the extremes of the property limits. However, attempts to fail batches intentionally is not easily done or indeed justifiable above the pilot scale. All of these issues assume that there is a method to measure key physical properties and that they may be correlated to the behavior of the material in the unit operation of impact. Many methods have, and are, being developed¹, although the traditional analytical methods are often insufficient for the development of a correlation with performance. A number of methods are currently under development at Purdue University, and two of these methods are discussed here.

Method for indexing crystals in morphology determination

Determination of the effect of crystal morphology on how the material will behave during handling is difficult to achieve.

Particle size, charging and morphology may interact, making it difficult to factor the contribution of each property to the observed behaviors. While there are reproducible methods for the measurement of size, for several reasons morphology is more difficult to measure. None of the current methods address the issue of determination of the crystal habit; that is, the crystallographic faces that are exhibited by the crystal. Morphology measurements made without this information ignore the possible differential characteristics of distinct faces.

Crystal faces have traditionally been indexed on one crystal that must be of relatively high quality. The methods of choice are optical goniometry, which determines interfacial angles, or obtaining the reflection on a single crystal unit with subsequent comparison to the known single crystal structure². The method used by the authors also requires knowledge of the single crystal structure; however, it is performed on a number of crystallites of varying quality. In addition, the method allows for the indexing of fragments of crystals, which may then be used to reconstruct the original morphology. This 'reverse' crystal engineering concept is in recognition of the fact that no matter how carefully one controls the morphology of the bulk drug, subsequent unit processes have the last word. An example that employs acetaminophen is described here, and it demonstrates both the utility and ease of the method. It is a simple way of determining the indices of crystal faces, and, because it is used on multiple crystals, the level of certainty of the index is high. This method is equally applicable to crystal fragments and the use of this in 'reverse crystal engineering' has also been reported³.

The method as executed consists of several steps.

- **Obtaining the single crystal data** – This is not usually an issue once the process development stage has been reached. The acetaminophen single crystal structure was obtained from Cambridge Structural Database (CSD). The reference code is HX-ACAN01 and it is the common polymorph, which crystallizes in the $P2_1/c$ space group.
- **Simulating the powder pattern from the single crystal data** – The powder pattern was simulated using the diffraction module in Cerius² (Molecular Simulations, Inc., San Diego, CA, USA) and the experimental patterns were subsequently 'indexed' from this reference.
- **'Picking' crystals and fragments** – The samples were prepared by picking approximately 10–25 crystals or fragments of crystals from a sample under the microscope.
- **Mounting the crystals and fragments on a powder x-ray diffraction (PXRD) cell** – These were mounted on a PXRD sample cell (with adhesion required for orientation) oriented with the face(s) in question parallel to the cell plane.
- **Performing an appropriate PXRD scan** – A PXRD scan was then run over the angular 2θ range of interest on a Shimadzu 6000

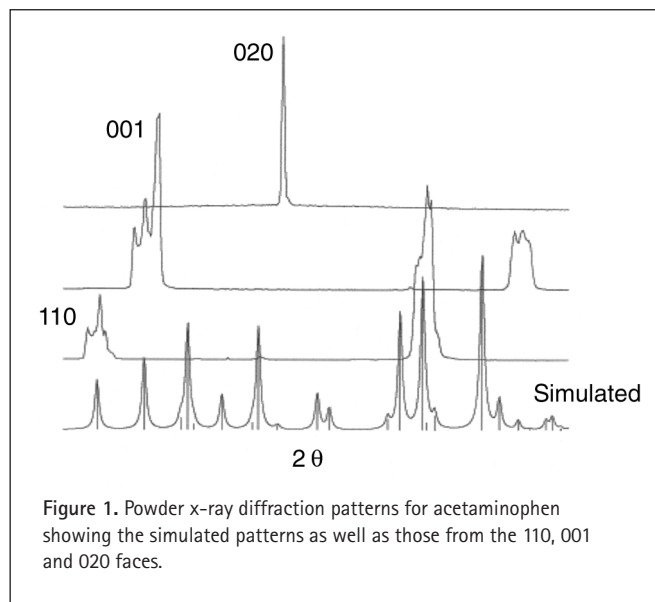


Figure 1. Powder x-ray diffraction patterns for acetaminophen showing the simulated patterns as well as those from the 110, 001 and 020 faces.

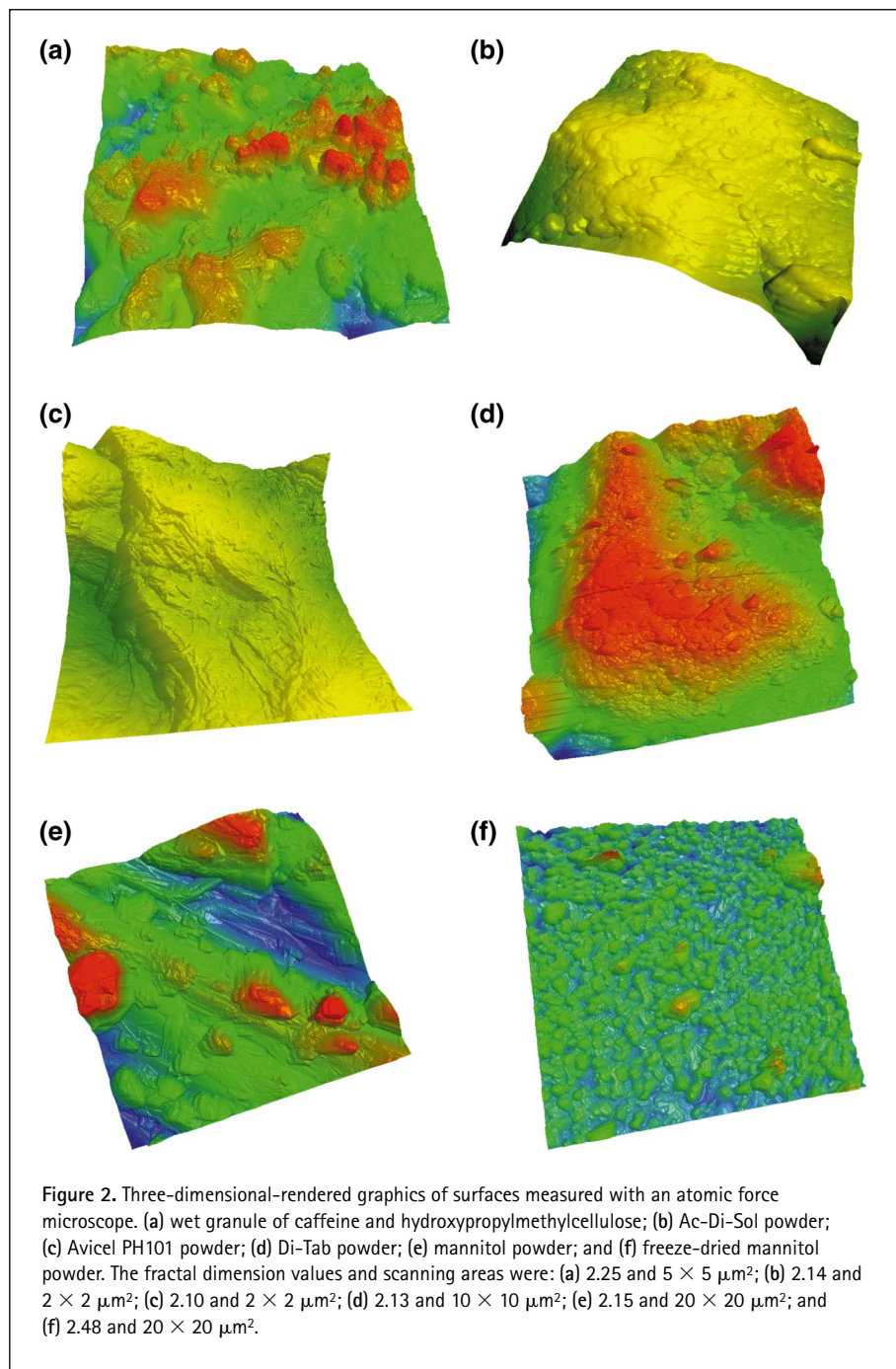
diffractometer. Alternately, or in addition, an omega scan can be used to allow for slight miss-alignment of the crystal(s). The crystals are oriented on what appears to be the same face, a run is performed, the crystals are re-oriented, and another pattern is collected. This sequence is repeated until all the major faces have been scanned.

- **Comparing the data to the simulated pattern for identification of the index** – Figure 1 shows the PXRD patterns for the oriented crystals and the simulated powder pattern. The Miller indices are determined from the simulated pattern. By matching the simple patterns from the oriented crystals, the faces are identified as the 110, 001 and 020 faces, respectively. The patterns can show multiple peaks at the expected angle due to height differences in these rather large crystals (300–500 μm). Also, note that there are two peaks in the 110 and 001 patterns due to the 220 and 002 planes representing the same family. The 020 is not preceded by an 010 peak because this is a systematic absence in the $P2_1/c$ space group.
- **Simulated morphologies may then be used to 'match' the observed habit** – The morphology predictor in Cerius² was used to obtain an approximate morphology for the acetaminophen crystals. The predictor uses the single crystal structure and a combination of some simple laws of crystal growth and attachment energy differences to simulate both the size and identity of the most probable faces. This was used both to aid in 'indexing' the faces and as a starting point to match the observed morphologies to possible simulated morphologies by achieving computational 'growth' of certain faces in a preferential manner.

Fractal analysis of pharmaceutical particles

Characterization of physical properties of pharmaceutical materials is important because the physical properties of

individual particles may be related to bulk properties. For example, flowability is known to be affected by morphological properties, such as particle size, particle shape and surface irregularity. Although a number of methods are available for characterization of particle size and shape, methods for the characterization of the surface irregularity or roughness are still poorly established. The authors used fractal analysis to characterize the surface roughness of pharmaceutical solid materials. The basic theory of fractal analysis, developed by Mandelbrot in 1977⁴, explains that the method is a resolution analysis that tracks the recurrence of topographical surface at different length scales. Traditional Euclidean geometry depicts a perfect straight line as a one-dimensional feature, an ideal plane as a two-dimensional feature and an ideal cube as a three-dimensional feature. Fractal dimension is a universal number that can be used for numerical evaluation of the degree of surface irregularity or the space-filling ability. It has been found that the surface and interface topographies of a large number of materials are fractals at the molecular level, and fractal analysis has become a widely accepted approach for the evaluation of surface roughness. In the study performed by the authors, the surface profile or topography was measured with an atomic force microscope (AFM). For several years, the AFM has demonstrated powerful functionality in many research areas, including surface roughness characterization. The benefit of using an AFM is that it is possible to obtain the surface profiles at the nanometer scale. It has been shown that the commonly used box-counting method is unsuitable and the power spectrum method generates relatively low-precision fractal dimensions for the digitized data. Thus, for the calculation of fractal dimension using digital data obtained from AFM, it was possible to implement the variation method⁵. The authors have used both box-counting and variation methods and found that the latter is superior in attempts to calculate the fractal dimension from the AFM data.



The surfaces of a range of pharmaceutical particles and granules were examined by an AFM (NanoScope-Multi-Mode, Digital Instruments, Inc., Santa Barbara, CA, USA) and their fractal dimensions were calculated. Figure 2 shows AFM images of a wet granule, Ac-Di-Sol powder (croscarmellose sodium, FMC, Newark, DE, USA), Avicel PH101 powder (microcrystalline cellulose, FMC), Di-Tab powder (dibasic calcium phosphate dihydrate, Rhône-Poulenc, Cranbury, NJ, USA), and mannitol powder (Mallinckrodt Baker, Paris, KY, USA) before and after freeze

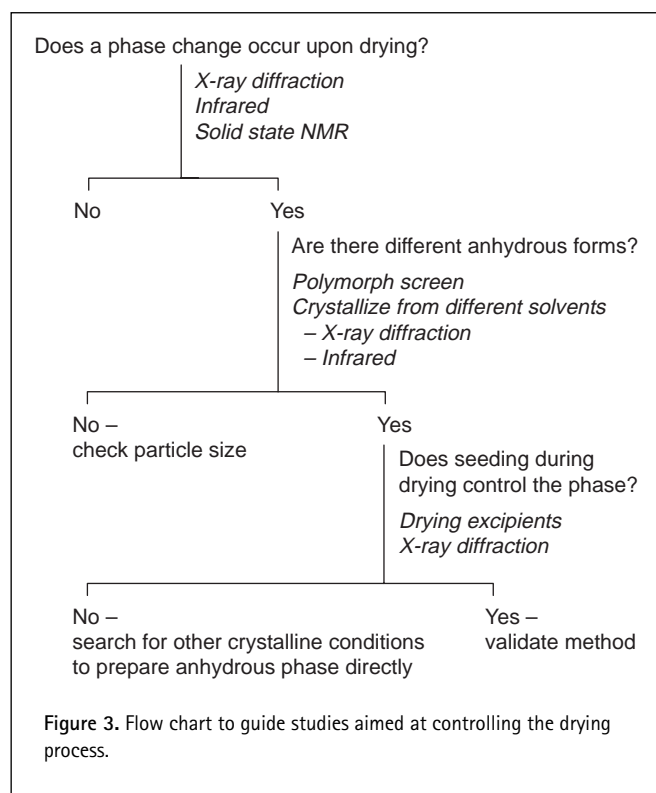
drying. As shown in Fig. 2(a)–(e), the fractal dimensions of all particles and granules were in the range of 2.1 and 2.3. This may be due to the fact that most of the pharmaceutical particles and granules were placed under similar processing conditions and this resulted in similar levels of surface roughness. When mannitol particles were freeze-dried, however, the fractal dimension was changed dramatically. As shown in Fig. 2(f), the AFM image of freeze-dried mannitol was quite different from that of the control mannitol. Such a difference is shown by the significant change in the fractal dimension. The surface of the freeze-dried mannitol sample was much rougher and the fractal dimension became significantly larger. In addition, the surface texture appeared to be changed by the freeze drying process. Figure 2(e) shows needle-shaped mannitol crystals on the surfaces, whereas no such mannitol crystals were observed on the freeze-dried mannitol surfaces [Fig. 2(f)]. These images demonstrated the ability of AFM to probe and obtain the three-dimensional surface profiles at the nanoscale. The results obtained by the authors in the fractal analysis of pharmaceutical samples revealed the existence of an intrinsic relationship between the fractal dimension and the underlying processes that produced the material and formed the surface morphology. It would appear that the fractal analysis using AFM can be used to quantify the surface roughness and to characterize pharmaceutical materials⁶.

Issues in bulk drug manufacture

Once specifications and methods have been established for raw materials, the unit processes involved in their production can be examined for possible improvement or change. The current focus is often on understanding possible solid-state transformations during final crystallization. Crystal engineering is an emerging technique that is designed to produce a narrow size distribution of crystals with a desired 'shape' or morphology.

Drying of hydrates and solvates

Drying is one of the last steps in bulk drug synthesis. Once the drug substance is crystallized, it is dried to produce the final drug substance. Drying is a unit process that can result in the loss of control of the manufacturing process for the drug substance, often resulting in lot failures due to unspecified polymorph and/or unsuitable particle size. Drying is particularly problematic if a hydrate or solvate is dried in this final step. Drying is even more problematic if a hydrate or solvate is dried to an anhydrous form in cases in which the anhydrous drug substance exists in multiple polymorphs. In these cases different polymorphs can be formed due to statistical variations involving nucleation of different polymorphs. In order to understand more about the drying process, the authors have studied the drying of phenobarbital. Phenobarbital (5-ethyl-5-phenylbarbituric acid)



has been reported to crystallize in as many as 13 modifications^{7,8}, and many of these forms were obtained by recrystallization with low levels of other barbiturates. More recent work suggests that there are four modifications of pure phenobarbital that are relevant to pharmaceutical processing⁹. Two of these forms are polymorphs (Form A and B) whereas the other two have been identified as a monohydrate and a hemihydrate. In an investigation of the physiochemical stability of these forms at different temperature and relative humidity (RH) levels, it is concluded that the drying of the hydrated forms yields a mixture of polymorphs. With this background, the primary objective of this project is to understand how a unit operation, such as drying, determines which solid state form is obtained and the factors that are instrumental in producing the desired form.

In the first instance, the various polymorphs were prepared and the effects of drying at various temperatures were evaluated. For these experiments the phenobarbital monohydrate or hemihydrate was dried at a controlled temperature and humidity in a laboratory oven. The products were analysed by x-ray powder diffraction, and visual comparison of the diffractograms was used to determine the final polymorphs present. The hemihydrate changes to a mixture of Forms A and B after storage for three hours at 50°C and 0% RH. The appearance of the mixture remains constant when drying is extended up to 15 days, and only when the hemihydrate is heated to 100°C is it possible to observe a transformation to Form B. The behavior of the monohydrate upon storage at 50°C and 0% RH is essentially

the same as the hemihydrate. A mixture of forms A and B is observed after several hours and this composition is unchanged after 30 days of storage. Similar results occur whether the monohydrate was prepared by the wet milling of either Form A or B.

In summary, it is clear that drying of either of these hydrates results in mixtures of crystal forms. Consultation of the flow charts in the International Conference on Harmonization Q6A Draft Guidance on Specifications establishes that such a process is out of control and would be problematic for the production of bulk drug substance. Additional studies are in progress to find ways to control the drying process and to control the crystal form. Figure 3 contains a flow chart, based on this research, to offer guidance in the drying process. This flow chart should be used to help avoid instances in which drying is an uncontrolled step in the production of drug substances or drug products.

Processing and process control

Control of processes has been both a concern and a strong point within the pharmaceutical industry. Pharmaceutical scientists operate under some of the strictest guidelines in existence and have done well in attempts to develop expertise to achieve control of the processes in current use. The approaches for the future have the general character of trying to transfer the expertise, in part, to monitoring systems. This may take much of the subjectivity out of the determination of processing control and makes it easier for regulatory agencies to verify the validation activities with less review. It may also require less specific experience by the operator to execute the process and thus help to reduce dependence on individuals for production. The acceptance of new processing techniques is slower because of both the high degree of reliability that must be demonstrated and the associated costs. Two examples of new technologies in development are roller compaction and supercritical fluid (SCF) particle size reduction. Roller compaction is being used increasingly in production sites, whereas SCF techniques are only now becoming a practical option (for example, they are in use at Bradford Particle Design in the UK and in the work presented here). Whatever the control and processing issues, the two are inexorably linked as more sophisticated processes require more advanced monitoring in order to maintain control. Linking all of these advances with computer integration suggests the possibility of achieving parametric release of product: this means less analysis cost, resources and time, as well as full tracking of the physico-chemical and equipment parameters throughout the production process.

Near-infrared determination of water in formulations

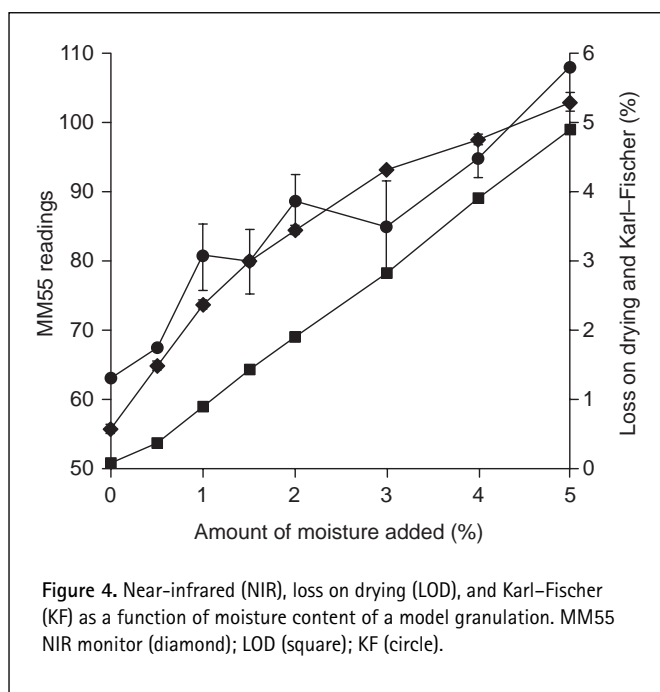
The determination of moisture in materials was the first application of near-infrared (NIR) spectroscopy and this remains its

most important use. Because of the improvement in NIR instrumentation and the ongoing research in this field, this method is now increasingly applied in the analysis of a range of pharmaceutical systems and problems, and NIR can be a useful technique in process and quality control¹⁰⁻¹⁸. NIR measures the overtones and combinations of the vibrational modes of a molecule, principally those involving bonds with hydrogen (i.e. C-H, N-H and O-H). Because of the low absorptivities of these bands, in contrast to mid-infrared measurements samples need not be diluted. Furthermore, NIR radiation is not absorbed by ordinary glass and is readily scattered by particles. Thus diffuse-reflectance spectroscopy is the most prominent sampling technique for solids and it is therefore well suited for on-line process monitoring. Finally, NIR spectroscopy may be a low cost method because it is non-destructive, fast and requires no special sample preparation.

The absorption spectrum of pure water shows, in the main, two strong absorption bands in the NIR region of ~750–2500 nm (4000–13,330 cm^{-1}), one band at 1940 nm (5150 cm^{-1}), and one band at 1450 nm (6900 cm^{-1}). The peak position is temperature dependent and is shifted to higher frequencies when water associates with other molecules by hydrogen bonding. Quantification of water is based on the measurement of these bands and other reference values of the spectrum while applying a proper mathematical algorithm to minimize variabilities in the reflectances caused by, for example, particle-size effects.

Many commercial NIR-sensors, such as the MM55 (Infrared Engineering, Inc., Irwindale, CA, USA), have been designed for the on-line monitoring of water in materials¹⁹. These instruments are fast in response (real-time monitoring) and, because they combine signal processing and readout, they are compact and easy to handle. However, successful implementation in a continuous on-line process control requires intelligent location of the sensor as well as correct adaptation of certain process and instrumentation parameters based on experiments in the laboratory. Once these parameters and a calibration routine have been developed, the method is stable until there are changes in sample composition or dramatic changes in the process parameters. In the meantime, any process variations can be traced to their source and eliminated.

Effective processing in the manufacture of solid dosage forms requires emphasis to be placed on automation and rationalization of the different production steps (e.g. mixing, granulation, sieving and drying). This is realized by closed single-vessel procedures (e.g. fluid bed granulators and high shear granulators), which require fast real-time methods for the in-process control. In terms of the moisture control of these processes, the NIR method is vastly superior to the traditional methods of loss on drying (LOD) or Karl-Fischer (KF)



titration. This is true even when at-line measurements are performed (sampling during processing). Both traditional assay methods are time consuming. Furthermore, a consequence of their application is the delay in receiving the analytical results. The time required for LOD may be several hours when low melting ingredients are manufactured and may not be applicable for detection of the entire amount of water, whereas KF-titration²⁰ has recognized limitations for molecules with certain functional groups (aldehydes, ketones, mercaptanes, etc.). Moreover, sampling is critical because of the small amount used for the titration, particularly when coulometric titration is performed, and reference values based on one of these methods are required for comparison during the development and calibration of the NIR method.

For processes such as granulation and drying, relative NIR values obtained from extremely fast-responding instruments with few narrow-band filters (such as the MM55), are sufficient to follow the moisture changes during the complete processing cycle. This is true even if the signal might slightly deviate from an ideal line because of changes in the water state (bound and unbound) and particle-size effects. Figure 4 shows an example for the analysis of granulated material (containing known amounts of water) using traditional and NIR methods. From this figure it is clear that LOD and KF both give linear fits to the data, although there is considerable noise in the KF data because of the sample sizes used (100 mg). The MM55 data shows a non-linear curve in which the first portion of the curve correlates with the bound water and the second portion of the curve correlates with the unbound water in the sample.

Because the MM55 data is very reproducible, NIR can be used to supplant KF or LOD measurements once a calibration curve has been produced for the process.

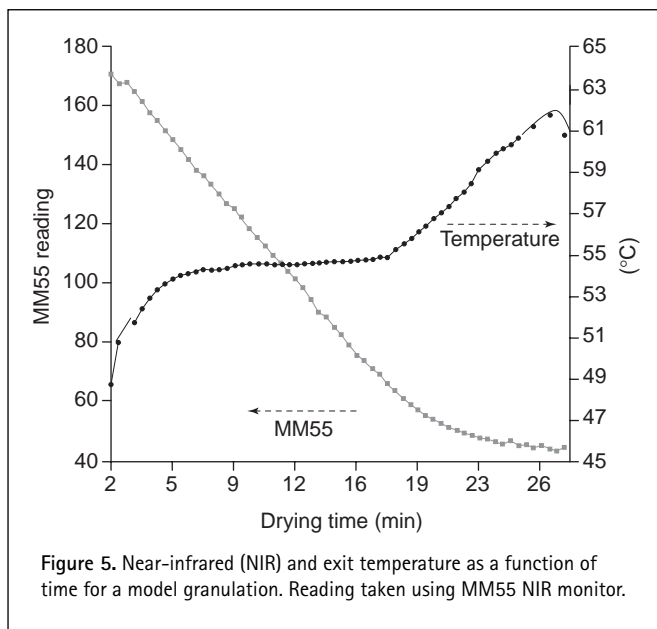
NIR monitoring of fluid bed drying

Fluid bed drying relies on established principles of both thermodynamics and the mass and heat transfer characteristic of the fluid bed dryer. The evaporation of water during drying requires heat energy. It receives this heat from the incoming airflow, which has the effect of 'cooling' the air. When there is little or no water left to evaporate, the exit-air temperature increases to the inlet-air temperature, which has been the traditional signal for the end of the drying process. During the evaporative cooling stage, the material in the bed is also cooled. The water evaporates off the surface, reducing the air temperature before the material comes into contact with the higher temperature.

The historical limitation to real time optimization and control of the process has been the inability to monitor anything dynamically, apart from the temperatures (inlet, bed and outlet, which are essentially constant until the very end of the process), or exit RH. This can lead to 'overshooting' the critical point and putting the process at risk or at least lengthening the cycle time. NIR methods use the MM55 monitor to follow fluid bed drying and this has increased the accuracy of attempts to determine critical process endpoints. Although real time monitoring is now coming of age, the general mass and heat transport principles underlying the fluid-bed drying process are well understood²¹.

There are typically two 'stages' during the fluid-bed drying process for typical pharmaceutical granules. These are defined by the rate limiting process involved with the loss of water. The first stage is heat transfer limited, which occurs throughout the period in which surface- or loosely associated water is evaporating from the surface of particles. The second stage is diffusion-limited, which occurs as the water within the granules must diffuse to the surface of the granule before it can be lost. Each of these processes is characterized by a different time dependence. The dependence of moisture content with time during stage one is linear, whereas the dependence during stage two is exponential for spherical particles.

Data on a model system. This dual-drying behavior (linear followed by exponential) is present in most of the MM55 NIR curves generated in our recently completed drying project. An example curve for a model high-dose active granulation dried at 60°C illustrates the point. Figure 5 shows the MM55 vs time and the exit temperature vs time for the system. This is a starch-based formulation granulated in a planetary mixer and dried in a UNI-GLATT fluid bed dryer (Glatt AirTechniques Inc., Ramsey, NJ, USA). The drying was monitored with the MM55 NIR monitor.



The temperature during drying is, as expected, relatively constant during the evaporative cooling region and rises as diffusion becomes a limiting factor. The critical point at which the drying process changes from linear to exponential (evaporative to diffusion limited) can be found by regressing the linear region point by point until the correlation coefficient starts to decrease.

The drying process may be simulated in each region through the use of physical constants and equipment and experimental parameters. It is in the linear region that this is most useful because it gives a minimum extrapolated drying time and allows adjustment of processing parameters to speed up the process within acceptable boundary conditions for the formulation. The dependence of moisture content (M) with time during stage one may be represented by the following equation:

$$M = M_0 - Kt \tag{1}$$

where K is a constant at a given temperature and includes terms for the gas density, bed height and heat of vaporization.

In terms of the model system used in this study, tabulated values for heat capacity and density of air and latent heat of vaporization of water were employed while the flow rate, equipment dimensions, and formulation variables (mass, density, void fraction, bed volume, temperatures) were taken from the manufacturer literature, estimated and measured, respectively. The simulated slope for this (linear) process is -1.28×10^{-4} and the experimental value is -1.25×10^{-4} . This is excellent agreement, given the uncertainty in some of the parameter estimates, and illustrates the utility of both the model and the monitoring activity. Thus, for a given inlet temperature, dryer and formulation, NIR monitoring provides a totally non-invasive

method for following the drying process. This facilitates both the identification of the mechanism of drying and control in any region of the process. Historically, such studies were difficult to perform, subject to sampling artifact, or required elaborate control for good water activity measurement.

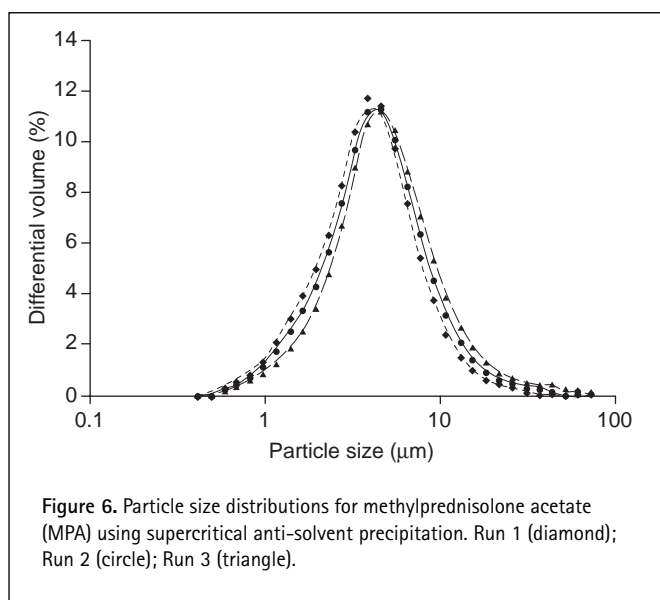
With the NIR information, optimization is accelerated, meaningful specifications can be established to keep the process under strict control, and the time usually needed to perform off-line monitoring is reduced or eliminated. The reduction in time needed for off-line analysis and release can decrease the process cycle time by significant amounts (as much as a 30% decrease in the authors' experience).

Supercritical fluid technology for particle size reduction

A uniformly small particle size and a narrow particle size distribution are often critical quality attributes of pharmaceutical solids, particularly for injectable suspensions and drugs intended for aerosol administration. The processing required to attain this, however, can adversely affect the physical properties of the drug, such as powder flow, agglomeration and suspension qualities. Most current methods for the reduction of particle size utilize mechanical methods, which cause a reduction in particle size by impact and attrition. The energy input from these operations may induce amorphous regions in crystalline material. A recent study documented subtle differences, induced by air jet micronization, in the crystallinity of albuterol sulfate. These differences were detected by analytical techniques such as water vapor sorption analysis, differential scanning calorimetry, microcalorimetry and laser light scattering²². The differences were attributed to amorphous regions imparted to the crystalline surfaces by the high energy input of air jet micronization. Water may be absorbed by the amorphous regions and lead to physical or chemical instability of the product during subsequent processing or storage.

An emerging unit operation for particle size reduction uses supercritical fluid technology to produce finely divided powders. One such method, supercritical antisolvent precipitation (SAS), accomplishes particle size reduction by using the supercritical fluid as a non-solvent to precipitate a drug from an organic solvent. The supercritical fluid, typically CO_2 , is at least partially miscible with the organic solvent. The CO_2 will cause high supersaturation ratios within the drug solution, forming many nuclei, leading to crystal growth. The mild conditions used in the process are favorable for most pharmaceutical compounds and the majority of the organic solvent may be extracted by using a continuous flow of CO_2 following precipitation.

The authors have constructed a pilot-scale apparatus for SAS precipitation, which is based on a design described by Schmitt²³. The system consists of a 2 L, jacketed, stirred autoclave as the precipitation vessel. A steady flow of CO_2 through the autoclave



is established using a 6000 PSI double-ended gas compressor. Constant system pressure is maintained by adjusting the flow of CO₂ using a pressure control valve. A feed solution containing a drug dissolved in an organic solvent is injected into the top of the autoclave by a double-headed, high pressure, metering pump through stainless steel tubing (0.0625 in O.D.). The supercritical fluid and organic solvent mixture exits through the bottom of the autoclave, leaving behind the precipitated drug. The precipitation vessel contains a collection basket, which is constructed to slide into the cylindrical bore of the autoclave. The bottom of the basket contains a removable 2 μm sintered stainless steel filter plate for collection of the precipitate.

Preliminary experiments, intended to identify critical process variables affecting particle size and particle size distribution, have examined feed solution temperature, CO₂ flow rate, feed solution flow rate, precipitation vessel temperature, vessel pressure, and agitation rate. The test system was methylprednisolone acetate in tetrahydrofuran (THF). Particle size distribution was measured by dynamic light scattering, and residual feed solvent levels were measured by gas chromatography. Results have shown the following:

- vessel pressure is the most important variable affecting particle size, with lower vessel pressures favoring smaller particle size distribution;
- the particle size distribution is quite reproducible when constant processing conditions are maintained (Fig. 6);
- residual THF levels were 0.0002% or less for all trial lots.

Adequate dispersion of the feed stream into the supercritical fluid appears to be important with respect to particle size distribution, and several options are being developed for equipment

modifications. In addition, further work is needed in order to understand how the feed solvent affects particle size of the SAS-precipitated powders.

End-product release based on in-process monitoring

Parametric release can be defined as the incorporation of validated in-line or on-line monitoring of key process variables throughout a production train to reproducibly generate final products. This has the effect of eliminating or reducing quality assurance (QA) and quality control (QC) resources required for product release and also ensuring product quality. Thus, parametric release would reduce the need for extensive, manual QA and QC testing.

There are several examples of final product release that could be done by in-process monitoring. Currently, sterile product preparation is monitored at a number of steps, including critical temperature of processing, container cleaning, fill monitoring of vials and water surveillance. Quick release of the end product requires rapid sterility testing, and this concept is currently under study. For solid dosage forms, in particular tablets made by wet granulation, monitors are required for the evaluation of the raw materials, mixing, wet granulation, drying, screening, mixing and compaction. The final tablets would then be observed with a suitable probe such as an infrared unit. This analysis has been reported for release of the dosage form, but what is needed is monitoring of the specific steps in the process. Consider, for example, a typical manufacturing process that involves mixing the bulk drug substance with excipients, wet granulation, drying, sieving, tableting and coating. Parametric release would involve the use of sensors to detect the end-point of mixing. Then, as the mixture is fed into the fluid-bed dryer for wet granulation and drying, the homogeneity of the mix would again be tested with a sensor. Another series of sensors would determine the end-point of the wet granulation and the end point of drying. As the dried granulation is sieved, sensors would again check the homogeneity and moisture content. As the sieved mixture flows into the tablet machine, the blend homogeneity would again be tested. Meanwhile particle size could be tested at several steps, as needed. Once the tablet core is made, sensors would check the content uniformity. Finally, the coating and drying process would be monitored by another set of sensors. The final product may need to be tested, although, after several months experience with such a process, it would be possible to statistically determine the correct process parameters and reject batches at any stage of the process.

Parametric release will reduce costs and the amount of manufacturer exposure. QC/QA costs will be minimized since the tests will be performed automatically. This will reduce process hold steps in which the process is stopped until a particular QC test is performed. Manufacturer exposure will be minimized

because all of the tests will be performed automatically with machines rather than sampling and subsequent analysis. Sampling issues will be minimized because many of the tests will be performed in-line. In addition, the availability of information from a range of sensors will provide improved monitoring of a process and allow more facile troubleshooting when problems arise. Parametric release will also reduce time-to-patient and speed scale-up of processes, and it will ensure more rigorous process uniformity than is currently found. This will ultimately lead to more uniform product quality and a better drug product. The importance of developing in-line sensors is highlighted and emphasized by the concept of parametric release. Indeed, the concept of parametric release provides a picture of the pharmaceutical manufacturing line of the 21st century.

Epilogue

In the short-term, there will be increasing emphasis within pharmaceutical manufacture on establishing meaningful physical specifications and methods for raw materials, as well as the use of advanced process monitoring techniques. The goal is better overall control and less waste due to rework and/or failed batches. The long-term view suggests that current novel production methods will become common due to a variety of technical and economic pressures. These techniques range from proven operations, such as roller compaction, to techniques for which new equipment will be required, such as super critical fluid precipitation. The vision of highly automated, controlled (yet rugged) processes with parametric release looks more realistic as the millennium approaches.

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