**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).**

**Kenneth R. Morris**
**Steven L. Nail**
**Garnet E. Peck**
**Stephen R. Byrn**
**Ulrich J. Griesser**
**Joseph G. Stowell**
**Sung-Joo Hwang**
**and Kinam Park***
Purdue University
School of Pharmacy
West Lafayette
IN 47907, USA
*tel: +1 765 494 7759
fax: +1 765 496 1903
e-mail:
esp@omni.cc.purdue.edu

▼ 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 do
new methodologies may b
development of the dosage fo

### *Compliance issues*

In addition to these consider
involve the US Food and D
(FDA) and its expectatio
documentation of new drug
ties. The agency's interest i
lation development and tec
sues has increased during i
post-approval inspections. T
are important in the design o
and equipment of the future
entists must consider what
quire in these areas. It is im
of the fact that FDA pays a g
to vendor sites and laborator
in a new product approval d
a great deal of emphasis is pla
manufacturing practices (cG
are committed to new drug
and abbreviated new drug ap
In terms of clinical trials,
records are important factor
new product's research and
scale-up and commercial pro

### *Analysis of unit operations*

Because unit operations may
to suit the requirements of
developers' activites in scale
will be carefully scrutinized
be aware of their processi
needs. As demonstrated in Ta
the activity centers around
cation and continuous effort
cations, which are often be

| | | | |
|---|---|---|---|
| | monitoring by thief sampling | Remote monitoring for endpoint determination | monitoring device |
| Dry granulation | High shear blending/slugging | Roller compaction<br>Uniformity monitoring | Full process contro<br>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)<br>Extrusion/sphearanization<br>Remote monitoring of granulation endpoint | Control of granule<br>real time modificat |
| Drying | Tray, fluid bed drying | Standard sampling and testing for water | Near infrared meth |
| Compression | Rotary tablet presses<br>Compression force or thickness priority | Fully instrumented presses | Feedback-controlle |
| Lyophylization | Empirically determined cycles | Cycle optimization using advanced analytical techniques | 'Smart' freeze dryer |
| End-product testing | Dissolution, hardness | Sampling | Final release by nea |
| Packaging | Semi-automated lines<br>Spot inspection | 100% inspection | |
| 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 wet granulation. Problems associated with wet make it necessary to adopt the dry granulatio order to achieve adequate control of the distrib tive ingredients. Advances have been made o years, although there is often inadequate contro ule characteristics, and there is a need to optir of wet granule formation. This will require cations of the process, or a second look at met have been discarded. The monitoring of the e granulation is still a technique of concern and v of monitoring the endpoint of wetting requi There is interest in the general monitoring o mization of tablet machines in current use, an into freeze-drying techniques for improved or preparation methods.

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

Conversely, a process is not in control
enough to be able to accommodate the n
ation of the physico-chemical properties
Some of the major issues surrounding phy
fication are listed in Box 1.

Lot-to-lot and batch-to-batch variation
raw material supplied by either an internal
also the result of a process with its own int
limits of variation should be defined for a
however, suppliers cannot be expected to c
ties that are of differing levels of import
facturer. Since multiple suppliers of a com
identified in the NDA, ANDA or supple
application (SNDA) stage, the variation i
from different suppliers must be examine
problem is representative sampling; that is,
tain analytical results on a small sample tha
characteristics of the bulk product. In term
second only to trying to obtain a represe
The results of lab- and/or pilot-scale testin
relationship to behavior at levels at the pro
fore, the range of acceptable variation mu
lished prior to technology transfer. It may
the limits by producing batches of produ
raw material that are at the extremes of
However, attempts to fail batches intent
done or indeed justifiable above the pilot
sues assume that there is a method to m
properties and that they may be correlate
the material in the unit operation of imp
have, and are, being developed[1], although
lytical methods are often insufficient for t
correlation with performance. A number
rently under development at Purdue Un
these methods are discussed here.

### *Method for indexing crystals in morphology*

Determination of the effect of crystal mor
material will behave during handling is

optical goniometry, which determines interfacial angles, or obtaining the reflection on a single crystal unit with subsequent comparison to the known single crystal structure[2]. 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 reported[3].

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 *Cerius*[2] (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 diffractometer. Alternately, or in addition, an
be used to allow for slight miss-alignment
The crystals are oriented on what appears
face, a run is performed, the crystals are re-o
other pattern is collected. This sequence is r
the major faces have been scanned.
- *Comparing the data to the simulated pattern for identi*
– Figure 1 shows the PXRD patterns for the
and the simulated powder pattern. The Mille
termined from the simulated pattern. By ma
ple patterns from the oriented crystals, the
fied as the 110, 001 and 020 faces, respectiv
can show multiple peaks at the expected ang
differences in these rather large crystals (
Also, note that there are two peaks in the 1
terns due to the 220 and 002 planes repres
family. The 020 is not preceded by an 010 p
is a systematic absence in the $P2_1/c$ space gr
- *Simulated morphologies may then be used to 'match' the*
morphology predictor in *Cerius*[2] was used t
proximate morphology for the acetaminopl
predictor uses the single crystal structure and
some simple laws of crystal growth and attach
ferences to simulate both the size and iden
probable faces. This was used both to aid in 'in
and as a starting point to match the observed
possible simulated morphologies by achievin
'growth' of certain faces in a preferential man

2θ

**Figure 1.** Powder x-ray diffraction patterns for acetami
showing the simulated patterns as well as those from t
and 020 faces.

### *Fractal analysis of pharmaceutical particles*

Characterization of physical properties of
materials is important because the physica

analysis to characterize the surface roughness of pharmaceutical solid materials. The basic theory of fractal analysis, developed by Mandelbrot in 1977[4], 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 form AFM, it was possible to implement the variation method[5]. 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.

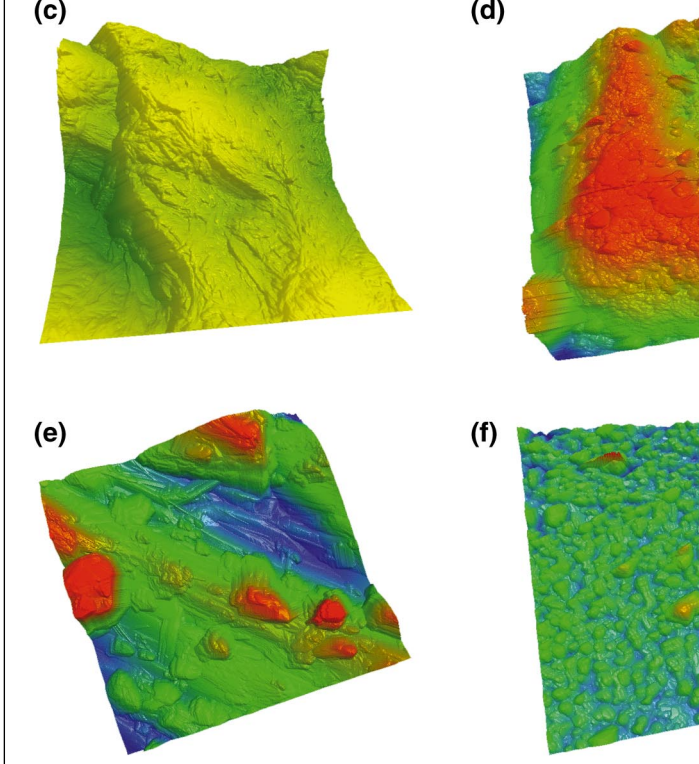


**Figure 2.** Three-dimensional-rendered graphics of surfaces measured with an at microscope. (a) wet granule of caffeine and hydroxypropylmethylcellulose; (b) Ac (c) Avicel PH101 powder; (d) Di-Tab powder; (e) mannitol powder; and (f) freeze- powder. The fractal dimension values and scanning areas were: (a) 2.25 and 5 × 2 × 2 μm²; (c) 2.10 and 2 × 2 μm²; (d) 2.13 and 10 × 10 μm²; (e) 2.15 and 20 (f) 2.48 and 20 × 20 μm².

The surfaces of a range of pharmaceutic ules were examined by an AFM (NanoScop tal Instruments, Inc., Santa Barbara, CA, U dimensions were calculated. Figure 2 sho wet granule, Ac-Di-Sol powder (croscarm Newark, DE, USA), Avicel PH101 powder ( lulose, FMC), Di-Tab powder (dibasic calci drate, Rhône-Poulenc, Cranbury, NJ, USA) der (Mallinckrodt Baker, Paris, KY, USA) be

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.