very solid-dose formulation team starts out aiming for a direct-compression tablet. It’s the most straightforward, easiest to control, and least expensive manufacturing option. Direct compression, of course, uses two primary process steps, mixing and compression, to produce the finished tablet. Wet granulation adds five more operations: wet granulation, wet milling, drying, milling, and mixing again. Each additional step requires equipment, operators, space, power, and expense…and every step lowers the yield and increases the risk of out-of-specification product.

So the most attractive solution almost always is the familiar, undramatic standby, direct compression.

“The basic tablet press has been fill, compress, and eject since about 1875,” says a veteran equipment marketer. “Ever since then, it’s been a matter of how do you control it better and now how do you clean it better.”

Yet, at last November’s annual meeting of the American Association of Pharmaceutical Scientists (AAPS), a crowd of hundreds overflowed the Baltimore Convention Center’s largest meeting room for the session that promised “New Developments in Direct Compression.” Why the standing-room-only attention right now?

“It’s not ‘right now;’ says consultant Metin Çelik, PhD, (Belle Mead, NJ, www.pt-int.com). “Direct compression is always there.”

Larry L. Augsburger, PhD, professor of pharmaceutics at the University of Maryland (Baltimore, MD, www.umaryland.edu), studies solid oral dosages. “You probably have a lot of people hoping to learn something,” he said. “They’re trying to expand to a broader range of drug loading. And you might have a lot of people who don’t have a basic grounding in the pharmaceutical sciences.”

Direct compression is easier and more economical…when it works. Or, rather, when it works within the allowable time.

**Time vs. money**

Time pressures vary over the drug-making continuum, from time-sensitive, high-margin new prescription drugs at one end to durable, low-margin over-the-counter and nutraceutical formulations at the other.

For a new prescription product, every day or week lost in formulation wastes irretrievable patent life. Speed, consistency, and reproducibility are the watchwords. So formulators spend relatively little time trying to attain a successful direct compression before moving on to easier-to-develop wet-granulation techniques.

“Every time we have a development project, we start with direct compression,” says Gary Bubb, vice-president of SMI (Lebanon, NJ, www.smitmc.com), a vendor of tablet presses and controls. In the end, though, he estimates that perhaps 80% of NDA projects wind up as wet granulations. “The decision is primarily driven by timelines rather than by cost. If I had a tight deadline, for example, I would do a wet granulation. It’s the most forgiving and most likely to succeed. I might not even explore anything else, unless I’ve got the resources so that I can explore things in parallel,” Bubb explains.

In generic drug formulations, time pressure is lower and cost pressure is higher. The products have lower margins and the processes will generally run longer. Reducing costs *via* direct compression can have a bigger proportionate impact on total profits. In this environment, says Ruey-Ching (Richard) Hwang, PhD, a senior director of pharmaceutical sciences at Pfizer Global Research and Development (Kalamazoo, MI, www.pfizer.com), “more than 50% of the generic formulations I’ve worked on use direct compression. About 30 to 40% wind up using wet granulation. And, 10% or less use roller
**Table I: Direct compression pitfalls.**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Effect</th>
<th>Key factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor blend uniformity</td>
<td>Inconsistent tablets</td>
<td>Particle size and shape, mixer design, poor blending design, segregation during handling</td>
</tr>
<tr>
<td>Erratic powder flow</td>
<td>Tablet weight variation, press adjustments, low press speeds</td>
<td>Particle size and shape, equipment design, high internal friction, external friction with vessel walls</td>
</tr>
<tr>
<td>Low blend density</td>
<td>Difficulty achieving tablet weight, press feeding problems</td>
<td>Density, true and bulk</td>
</tr>
<tr>
<td>Poor compressibility</td>
<td>High punch forces, soft tablets</td>
<td>Particle size and shape, powder ductility, tooling design, press set up</td>
</tr>
<tr>
<td>Mechanical weakness</td>
<td>Friability, logo picking, erosion during coating</td>
<td>Particle size and shape, tensile strength, tooling design, press set up</td>
</tr>
</tbody>
</table>


compaction.” Hwang calls this last technique “underutilized.”

For the most part, though, formulators can only look with envy on the direct-compression success reportedly achieved by Johnson & Johnson’s former development director, Paul E. Wray. “He spent his entire life doing formulation development,” says one equipment maker who worked with him, “and in his entire career never had one product that was not direct compression: If you fight long enough and work hard enough and don’t take the lazy way out, you can make it work.”

**Signposts for successful compression**

What are the barriers to a successful direct-compression formulation and what can go wrong after the process goes into production?

At AAPS, Pfizer research fellow Bruno C. Hancock cautioned the audience with an outline of Things That Can Go Wrong with Direct Compression (see Table I). Hancock emphasizes how important it is to understand the properties of the blended active pharmaceutical ingredient (API) and excipients, starting with particle shape and size distribution, friction and adhesion profiles, true and bulk densities, compaction parameters, and compacted mechanical properties.

Four factors are critical in a manufacturable direct-compression formulation, Hwang says: blend uniformity, blend flowability (especially at the rates demanded by high-speed presses), compressibility, and lubricity. Of these, the most important is flowability, though the property is disturbingly difficult to quantify. It can be measured as an angle of repose or effective internal friction (a small angle is good; a large angle is bad) or by flow rates and performance in a test funnel or hopper (mass flow, good; rat-holing, bad). The flow-rate tests, however, depend on the size, shape, and even the material of the test vessel in a way that would make a theoretical physicist cringe.

Workers in the field often hesitate to cite specific cut-off values for these key properties; Hancock does not. His AAPS presentation culminated by listing, and quantifying, the hallmarks of an ideal direct-compression material (see Table II).

Without well-established, well-quantified indices to distinguish good blends from bad, formulators must fall back on experiment. Armed with sufficient API and excipient materials and a design-of-experiments approach, Hwang says, a formulator should know whether a direct-compression formulation is feasible after two sets of studies, consisting of 10–20 experiments each. (The whole program might take a month or two.)

**Understanding excipients...better**

Ultimately, expanding the useful range of direct compression requires expanding our understanding of how the APIs and excipients behave as bulk powders and under compression, transforming the current qualitative and subjective judgments of “good” into quantified, predictive parameters.

“There’s a growing body of information cataloging the physical properties of directly compressible materials, but the information is scattered,” says Augsburger. “For example there have been some recent papers on using multiple methods or indices to characterize the flowability of direct-compression fillers. Instead of saying, ‘This is a very compressible excipient,’ you

**Table II: Properties of an ideal direct-compression material.**

<table>
<thead>
<tr>
<th>Property</th>
<th>Parameter</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size and shape</td>
<td>D 4,3 (mean volume diameter)</td>
<td>&gt;80 µm</td>
</tr>
<tr>
<td></td>
<td>D 10 (10th percentile diameter)</td>
<td>&gt;30 µm</td>
</tr>
<tr>
<td></td>
<td>D 90 (90th percentile diameter)</td>
<td>&lt;1000 µm</td>
</tr>
<tr>
<td></td>
<td>Aspect ratio</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Blend uniformity</td>
<td>Blend potency</td>
<td>&lt;2% RSD*</td>
</tr>
<tr>
<td>Powder flow</td>
<td>Effective angle of internal friction</td>
<td>&lt;41*</td>
</tr>
<tr>
<td></td>
<td>True</td>
<td>&gt;0.5 g/ml</td>
</tr>
<tr>
<td></td>
<td>Bulk</td>
<td>1.0–2.5 g/ml</td>
</tr>
<tr>
<td>Tableting performance</td>
<td>Dwell time sensitivity</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Precompression force</td>
<td>Low</td>
</tr>
<tr>
<td>Compact mechanical properties</td>
<td>Compression stress (at ~0.85 solid fraction)</td>
<td>20–125 MPa</td>
</tr>
<tr>
<td></td>
<td>Tensile strength (at ~0.85 solid fraction)</td>
<td>&gt;1.0 MPa</td>
</tr>
<tr>
<td></td>
<td>Brittle fracture index (at ~0.85 solid fraction)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Indentation hardness (at ~0.85 solid fraction)</td>
<td>75–250 MPa</td>
</tr>
</tbody>
</table>

* RSD is relative standard deviation

might be able to say, ‘It has a bonding index of such and such and it has a flowability index of such and such,’ giving a better comparison for choosing and selecting. Even the concept of compactability is not well understood right now....”

Hwang notes that several industry research groups have mined their ingredient-characteristic and formulation-performance databases, trying to correlate standard ingredient-property measurements (including various indices of flowability) with later scale-up and manufacturing behavior. The resulting measures can give the formulator a ballpark expectation of success, “but there’s never a one-to-one correlation between index A and final behavior B,” says Hwang.

Hancock’s group has had some success using shear cells to quantify flow characteristics. It’s an old and sometimes cantankerous technology, he admits, but it yields more consistent and comparable data. Hancock notes that his laboratory builds about half of the research equipment they use, using what he calls a “science of scaling down.” Rather than begin with commercial analytical equipment and then scaling the formulation up, the Groton, CT, research group starts with manufacturing equipment and then builds laboratory-scale devices that mirror its behavior.

**Post-approval trauma**
The formulation challenges don’t end when the process is validated, up, and running.

Though the very thought of reformulating an approved product is anathema to most process managers, sometimes “reformulation is the easier way to go,” in the words of one excipient supplier. “In the short term, it’s expensive, especially if there is some bio work required to revalidate the process.” Still, reformulation may be the best, most economical, or indeed the only way to resuscitate a product that has gotten into regulatory trouble because of poor tablet consistency or physical defects.

Some tableting problems, says an equipment manufacturer, “are the result of just so much international sourcing of ingredients. Today the purchasing folks are under so much pressure that they buy this batch from here and that batch from there. Even though they pass quality control, their characteristics are not exactly the same. In production, you can’t get the batches to turn out the same no matter what you do to them.”

When a tableting process breaks down, the consequences can be dire. In the most recent case, federal marshals seized all stocks of two GlaxoSmithKline products for what appear to be tableting errors. (See news item on page 21.)

**Tableting in evolution**
“Though there have not been any impor-
tant developments in direct compression for pushing ten years,” says Augsburger, “there have been some innovations in the equipment. The evolutionary process goes on, but the basic technology depends on the excipients and whatever API you’re using.”

The important concentration in recent years has been in better machine management and better integration with the rest of the production process, says Dale Natoli, of tool-and-die maker Natoli Engineering (St. Charles, MO, www.natoli.com) “We’re not talking innovation here. We’re not talking new,“ he says. “We’re talking proper management.”

**Process analytical technologies (PAT).** If there is indeed a growing interest in the fundamentals of direct compression, the opportunities of process analytical technology may be responsible. “With fewer steps, and fewer process variables, the process should be easier to model, monitor, and control,” says Çelik.

Augsburger concurs. “It may sound like bandwagon stuff,” he says, “but I do think that some of the ideas being stimulated by PAT initiative—‘Hey, we’d better go back and understand our processes or formulations a whole lot better than we do now’—could have a payoff that’s significant. So now we have people scrambling to do basic pharmaceutics where they never did it before. It’s pretty exciting.”

Right now, tablet-press data-collection focuses on the product (controlling tablet-weight, for example) rather than on the machine (controlling operating temperatures or providing predictive maintenance). Even so, many tablet presses already provide more process information than the operators now use.

Data acquisition systems—original equipment or add-on—are available for old and new systems. They are capable of producing reams of data, like detailed curves of compression force vs. time for each tool, ejection forces, and stripping force. (Ejection force pops the tablet out of the die. Stripping force pushes it off the lower punch face.)

**Unused information.** In general, say most experts, the industry focuses on a single data stream: peak compression force. And most processes monitor just a single aspect of that: peak compression force variation. Low variation indicates consistent tablet weights; larger variations indicate that the amount of material filled into the die is inconsistent, so that tablet weights will vary.

The other data are ignored. “Unfortunately the industry doesn’t know what to do with this information,” says a press-maker. “Great, we’ve spent $60,000 or $80,000 or $100,000 and what do we do with it now? They have a lot of information they could use, and it’s not just looking for peaks.”

The compression-force curve alone contains a good deal of data that isn’t generally used. Dwell time is critical to ensuring proper compression: make it too short, and tablets are likely to cap (separate at the top layer) or laminate (separate at an internal layer). Roughness in the force curve can warn of undue friction in the punch or die, and indication of deformation and impending failure.

Ejection and stripping force readings...
can be useful diagnostics, says Natoli: these forces generally increase when heat—
generated by compression and friction—
builds up in the tooling.

The heating problem deserves more at-
tention, in Natoli’s view. “The biggest
problem in this industry is picking [small
particles adhering to the tool faces, result-
ing in small defects in engraved logos and
edges] and sticking [heavier material
buildup on the tooling],” Right now, Na-
toli says, researchers don’t know exactly
how much of the heat buildup inside the
punch is caused by friction and how much
is caused by the thermodynamics of com-
pression. Powders come together and
abrade across the punch face, he says, cre-
ating a superficial heat much higher on
the tool surface than it is inside the tool
or machine. Over time, operating temper-
ate rises, which can make product stick
to tool faces and die walls. The high tem-
perature can even burn the materials,
causing black specks and streaking of the
tablet’s side wall.

**Keeping it cool.** “We want the press to
run as cool as possible,” Natoli says. “If we
can reduce the amount of heat we’re cre-
ating, then we’re going to eliminate a lot
of tableting problems: sometimes …the
surface of the tool gets warm and the ma-
terial melts on the surface of the punch.
And these data acquisition systems can’t
detect that directly. They catch it when the
tablet-stripping force increases, and then
we realize that we’ve started to film. Once
we start to film, then we start to stick and
pick. We want to eliminate stick and pick,
and so we want to monitor tablet takeoff
and ejection forces.”

There are limits, of course, to how use-
ful these data can be in practice. Natoli ap-
plies a practical standard: “If you have a
problem product that tends to bind and
stick and [cause] premature tool wear,
then I would say it should be monitored
consistently.” If developers have produced
an efficient combination of blend, tool-
ing, and press set-up that runs fairly well,
then spot monitoring is sufficient.

**Containment, wash-in-place, and layering.**
The general manufacturing trends toward
process containment and washing-in-place
have commanded much of the press-
makers’ R&D attention over the past few
years. “Containment and wash-in-place
(WIP) have been a big deal,” says one in-
dustry observer. “All of the [upstream] op-
erations have been contained, so now we’re
moving to the end of the line, the final op-
eration is being contained, with WIP as
well.”

The move to containment goes hand in
hand with the increasing prevalence of
high-potency active ingredients and the
increasing focus on operator protection.

Containment clearly makes the plant
cleaner and easier to manage. So does WIP
equipment, which requires only minor
outward modifications in the design. For
WIP, “materials and construction have to
be compatible with the cleaning agents.
Windows have to be sealed properly. And
there has to be some way to remove the
water that makes sense. It doesn’t look dra-
matically different to a casual observer,
though,” the observer says.

He also notes an increasing interest in
multilayer tablets. “They’ve been around for many years and there’s nothing new in terms of feasibility,” he says, “but suddenly everybody seems to want to make them and make them for real.”

**Tooling trends**

It’s probably natural that Natoli, a tablet-tooling maker, feels that tooling often fails to get the process-management attention it deserves. Then again, the punch and die touch the tablet, and the tablet winds up in the customer’s hand bearing the imprints of that operation. Proper tool management is thus vital to consumer acceptance...as well as to the in-specification acceptance rate.

The evolution in tooling has centered on productivity and durability: multiple tool tips, new tool materials, and rotating punch heads.

**Multiple tool tips.** Multiple-tip tools produce more than one tablet per station per pass. With 10–99 stations and one or two passes per station per revolution, multiple tool tips with as many as four tablets per tool greatly increase the tablet production rate. These European-style tools, Natoli notes, have been common abroad for several years, but have been used in the United States only for the past five years. They do increase demands on the press: the total compression force increases as a multiple of the number of tablets in the die, and ejection and stripping forces increase as well.

Multiplied compression forces, faster press speeds, and multiple compression cycles all increase the wear on the tool head (i.e., the portion that rides in the guide tracks and contacts the tablet press’s compression rollers). Natoli’s company has responded by allowing the tool heads to rotate as they travel around the press, thereby spreading the wear over the whole tool head and lengthening head life.

**Tool materials.** For decades, machine shops have made pharmaceutical dies and punches from standard tool steels. Today’s compression tooling makers have just begun to explore powdered-metal and composite (e.g., high-density plastics) materials. “These are fairly new, so there’s a whole lot to be learned at this point; we’re just in the process of trying to reformulate these materials to tailor them for pharmaceutical compressions.” Natoli says.

Composite materials are available on what Natoli calls stronger tablet configurations (i.e., those with smaller cup depths). Designers go to deep cupping for esthetics—it makes the tablet appear smaller and easier to swallow. “It comes down to consumer acceptance,” Natoli says.

The deeper the cup on a tool, the weaker the cup edge. This increases the potential for distortion during compression, leading to brittle fracture along the punch edges. Flatter tablets have sharper corners, which give a stronger tooling configuration, but may give an appearance of being uncomfortable to swallow. The sharper corners of a flat tablet may increase chances of chipping: “The industry certainly believes that,” says Natoli, “but I don’t think this is always true.”

The important thing, he says, is communication between the tool manufacturer and the tablet maker, “and they’re not doing it as well as they should to provide a configuration that’s acceptable to marketing, consumers, and the tool manufacturer.”