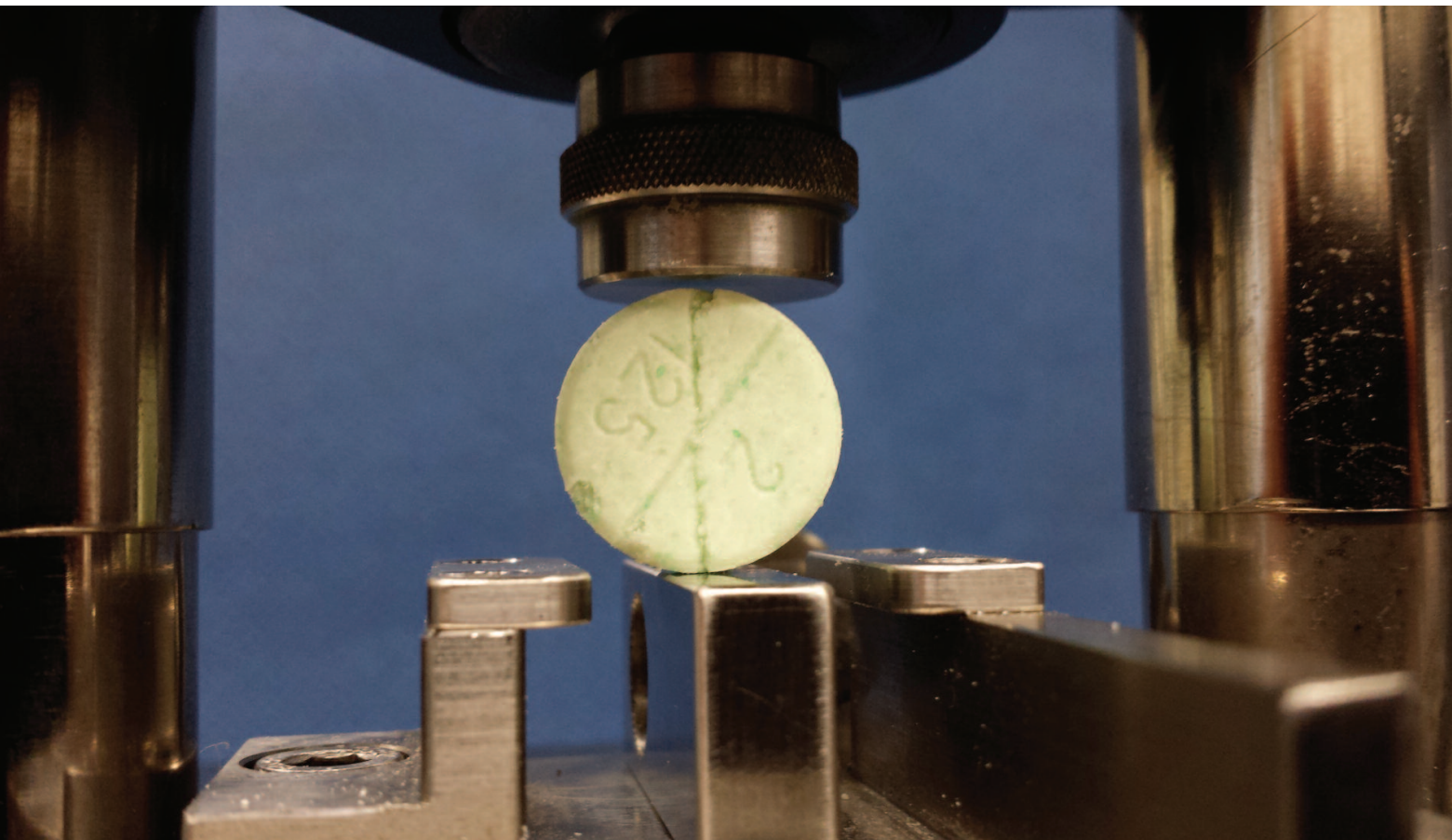


tableting

MAKING BETTER TABLETS: A QBD APPROACH

MICHAEL GAMLEN
GAMLEN TABLETING

JOE DOMINGUE
SCIMARK INTERNATIONAL



To improve the formulation development process, test the properties of tablet materials on an instrumented press early and often. In this article, the authors describe how a benchtop tablet press and material tester characterizes both tablets and materials to help you develop a robust formulation. It also touches on the shortcomings of the FDA's SUPAC guidances in improving existing tablet formulations.

Developing and manufacturing tablets are complex activities, as Joseph Woods noted more than a century ago:

The many difficulties constantly presenting themselves to the author and his assistants in the manufacture of tablets, and the marked absence of literature relating to the subject, have led to the preparation of this little volume [1].

Later in the book, he correctly identifies many of the key problems that afflict tablet production, such as capping, sticking, and picking, and pinpoints some of their causes. He also recommends solutions. See Table 1.

It is humbling to realize that, despite 108 years of scientific endeavor since the publication of Wood's book, we still cannot reliably identify the root causes of many tableting problems nor how to fix them. Our lack of progress in this area stems both from the nature of conventional tablet presses and from the traditional, century-old approach to tablet development.

Consider first the equipment. Regardless whether it's a single-punch lab press or a rotary production machine, the principle of operation is the same: Compress the material to a particular thickness. On a single-punch machine, the position of the upper punch determines the thickness, while on rotary presses, thickness depends on the distance between the upper and lower rollers. Small

TABLE 1

Causes of capping problems and methods of resolving them, as identified by Wood in 1906 [1]*

Cause	Solution
Imperfect upper punch	Replace
Imperfect or worn die	Replace
Imperfect alignment of punches or dies	Remedy machine setup
Too much pressure	Reduce pressure
Damp granulation	Reduce moisture content
Too much fine powder in granulation	Remove fines or increase granule size
Granulation too soft	Granulate to correct endpoint
Wrongly proportioned excipients	Correct over- or under-granulation. Re-granulate to form proper granules using a better binder. If formulation is too soluble, switch to solvent with lower solubility.

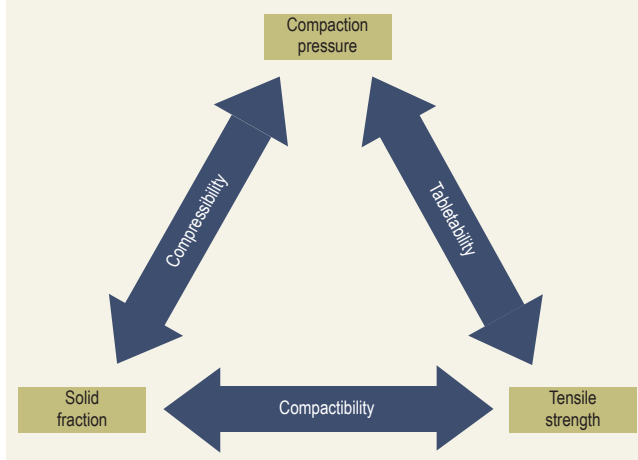
* At the time, all products were made by wet granulation.

differences in thickness—as little as a few tenths of a millimeter—can have a dramatic effect on other tablet properties.

That's why instead of thickness, it would be more practical to compress a series of tablets at different *forces* under otherwise similar conditions. By so doing, you could determine how compaction affects the tablet over a measured range of forces or pressures, which would enable you to fully characterize the material being compressed. Full characterization requires measuring three tablet parameters: compaction pressure, tensile fracture stress, and solid fraction. These three parameters form the "compaction triangle" shown in Figure 1 [2]. Each should be measured from the earliest stages of formulation and continuously throughout the tablet development process.

FIGURE 1

The compaction triangle [2]



The importance of an instrumented press

Determining tensile fracture stress (sometimes simply called tensile strength) entails measuring the load required to break the tablet under controlled conditions. Knowing the tablet's tensile strength is useful because the

value is a linear function of compaction pressure [3] up to a limiting value of pressure. As a result, once a formulation has been characterized, compacting a single tablet at a known pressure enables you to determine its compression properties. Likewise, the solid fraction of a tablet increases as compaction pressure increases, although that relationship is not linear. There are many cases cited in the literature of tablets with extremely high solid fractions: 0.95 or greater. Compaction under those conditions is likely to cause capping or delamination, and water penetration of the tablets will be poor. A solid fraction of 0.85 to 0.90 is optimal.

Pitt et al. [4] provide additional guidance for optimum performance, including a recommendation that tablets have a minimum strength of 2 megapascals (MPa) when compressed at a compaction pressure of 200 MPa, the maximum pressure that most tablet manufacturing operations recommend. The same study also recommends an ejection stress—calculated from the force needed to eject the tablet from the die—of not more than 5 MPa.

As Pitt's study and other recent data demonstrate, tablet development should follow a continuous, iterative process in which the formula and processing variations are systematically evaluated, in some cases using designed experiments, which the FDA has dubbed Quality by Design (QbD). But that's a difficult task for pharmaceutical scientists, most of whom have limited access to sophisticated compaction simulators and lack the expertise required to use them. Most of these simulators are found in a manufacturing environment, not the development lab. This lack of access and expertise led us to develop a benchtop laboratory tablet press (photo) [5]. It is a relatively inexpensive and easy-to-use lab-scale and at-line simulator that helps product development scientists and others who seek to optimize the process of making solid-state formulations. It also helps control quality and enables you to troubleshoot ingredient and batch-to-batch variations that contribute to tablet failures during manufacture.



Benchtop tablet press and material tester [5]

By using a benchtop tablet press, you can specify and control the force applied while the instrument records both the force and the punch position during compaction and ejection. It can display those parameters in real time.

The instrument also allows you to measure, using a hand-held force meter (photo), the detachment force (punch take-off force). That information is especially useful when studying lubrication processes. The benchtop unit can also measure tablet tensile strength.



Using a handheld gauge to measure detachment (take-off) force on a benchtop tablet press and material tester

By quickly testing a wide range of formulations—using small amounts of material—you can gain the insight Woods sought more than a century ago: “[T]he proper manipulation of the medicinal ingredients, and the choice, proportioning, and manipulation of excipients best suited to use with the different formulas require a considerable degree of skill, as well as an intimate knowledge of the physical and chemical properties of the ingredients” [6]. That summarizes the value of using a properly instrumented system: You gain the knowledge required in a consistent way, enabling you to formulate and manufacture good tablets.

Simulation and production equivalence

Tableting simulation also enables you to understand what occurs in a production environment. Indeed our work has shown that data from our benchtop tablet press simulate data generated on a production tablet press operating under actual production conditions. Specifically, we compared how two products—one a wet granulation and one a direct-compression granulation—performed on a Fette 2090 production tablet press and on our benchtop tablet press. The data showed an equivalence, which illustrated an important but seldom recognized fact: Over a wide range of tablet sizes and compaction pressures, the tensile fracture stress of a tablet is independent of tablet size and is determined solely by the compaction pressure.

Indeed, the study showed an equivalence between an 800-milligram capsule-shaped tablet and a flat-faced circular 100-milligram tablet 6 millimeters in diameter. The tensile fracture stresses of the capsule-shaped tablets—tested in longitudinal compression—were calculated using an analysis [7] that can determine the tensile fracture stress of tablets of almost any shape. We subsequently extended that analytic method to apply to cylindrical tablets as small

as 2 millimeters in diameter. In so doing, we learned that tensile fracture stress is size-independent in tablet diameters of 2 to 12 millimeters, at least for the materials we have tested to date, including lactose, starch 1500, microcrystalline cellulose, and many other proprietary formulations at pressures as high as 200 MPa.

Improving process development

The FDA’s QbD initiative correctly states that it is safer, more efficient, and more cost-effective to get a formulation right the first time and monitor its performance than it is to troubleshoot it or discard defective or poorly performing formulations. This is especially true once formulations are at an advanced stage. If not caught early, the problems only compound once poor formulations reach the manufacturing site.

To prevent problems, your formulation development process should include these steps:

Identify your company’s preferred manufacturing method. Seldom do companies decide which process they would prefer to use, but that should be done early in the developmental stage. After all, manufacturing costs increase significantly as a project moves from direct compression to dry granulation and, finally, to wet granulation. Unfortunately, the ability of the process to withstand variations in API or excipient properties follows the same order. That is, changes to direct-compression processes are most susceptible to upsets; dry-granulated formulations are a little more robust; and wet granulations cope with wide variation in properties. Find the right balance between the cost and robustness of your process and formulation.

Evaluate the process and formulation variables. This is now a regulatory expectation (and essential for an ANDA submission), but many companies still struggle with it. This is due partly to the difficulty of evaluating processed materials prepared on a small scale and partly to our lack of understanding of the key elements that underpin formulation science. For example, if a powder blend suffers from poor content uniformity, we cannot predict the effect on blend quality when we replace one excipient with another that is either more or less free flowing. In some cases, using a more free-flowing material will improve the product; other times it makes powder flow worse.

Develop a manufacturing control strategy. Document all development work and all prior knowledge about the formulation and process during development and manufacturing. No formulation is developed in a vacuum, and most companies have volumes of data about their manufacturing processes. Few, however, use these data to guide product development toward processes that will be both robust and low cost. It would be very useful, for example, to receive management updates about the performance of dry granulation processes (as a group) versus wet granulation processes. Which are in better control? Use that data to guide your selection of processes for future products.

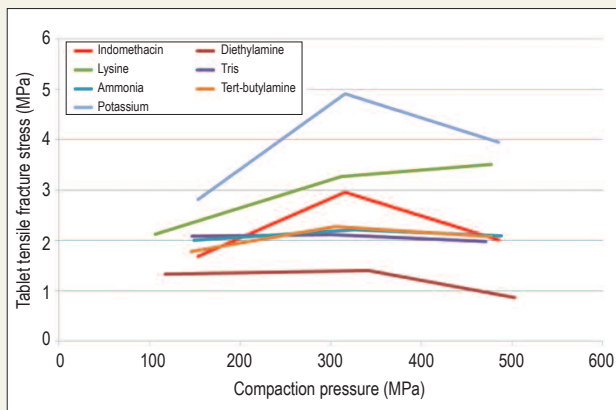
Recent studies

Last year at the annual meeting of the American Association of Pharmaceutical Scientists, we published three posters describing the utility and versatility of using our instrumented tablet press.

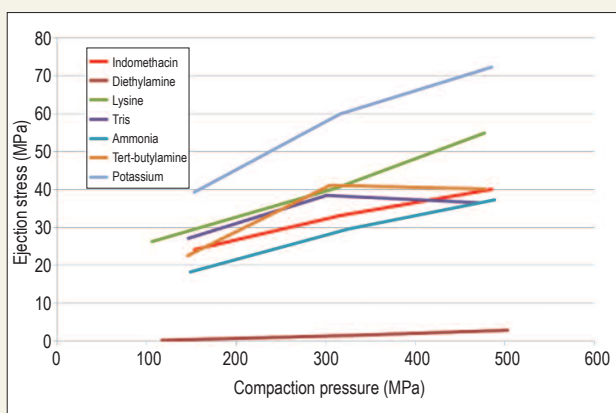
The first discussed part of a QbD-style drug-salt selection process in which small samples of a range of salts of indomethacin were prepared and characterized by x-ray powder diffraction and Raman spectroscopy [8]. Next, 10-milligram samples were compressed on the tablet press, which measured the compaction-ejection behavior; the press then fractured the compacts to measure “tablet-ability” (Figure 2). The results showed clear differences in the tableting behavior among the various salts and helped in selecting the optimal salt for tableting.

FIGURE 2

Tablet strength and ejection stresses of various indomethacin salts



a. Tensile fracture stress of indomethacin salt tablets



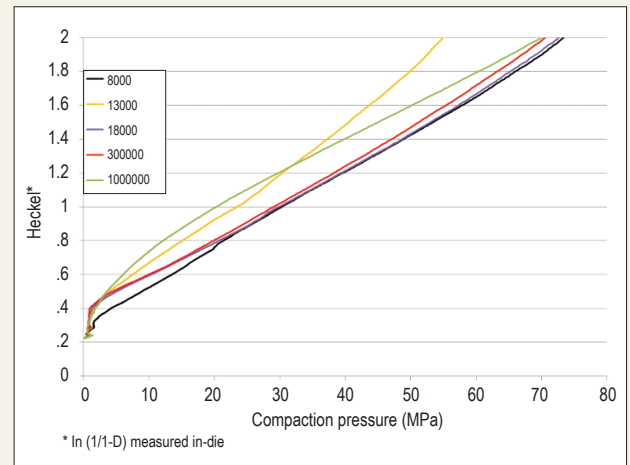
b. Ejection stress of indomethacin salt tablets

The second study focused on excipient compressibility [9]. A range of chitosans of different molecular weights were isolated and chemically characterized. Next, compression properties were evaluated using in-die and out-of-die Heckel testing, and the effect of molecular weight on compression properties was observed using displacement data, which the tablet press generated automatically

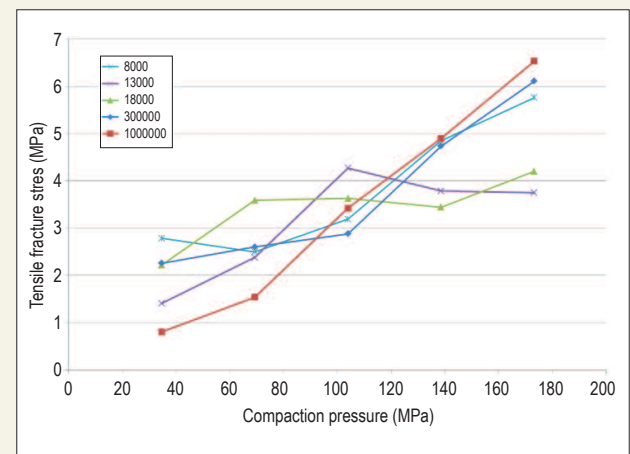
(Figure 3). The information—useful in understanding the underlying compaction mechanism of a material—helps formulators select the most appropriate formulation.

FIGURE 3

Heckel plots and tablet strength profiles of different chitosan samples



a. Heckel plot (measured in the die)



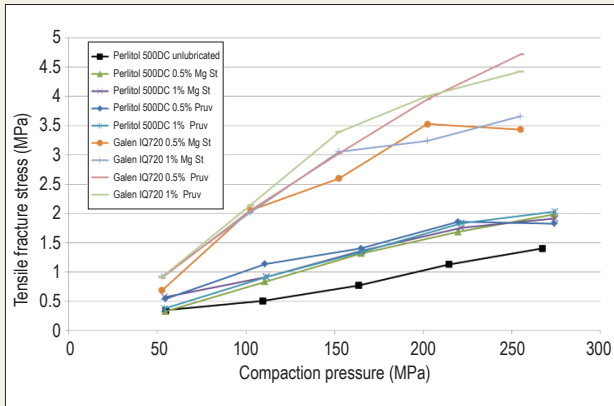
b. Tensile fracture stress

The final poster addressed formulation selection based on the measurement of tablet ejection and detachment forces [10]. The results were both interesting and unexpected. The study used a range of excipients lubricated with two popular lubricants: magnesium stearate and sodium stearyl fumarate. Tablets were then prepared and subsequently evaluated for compression, ejection and detachment stresses, and tablet tensile fracture stress (Figure 4).

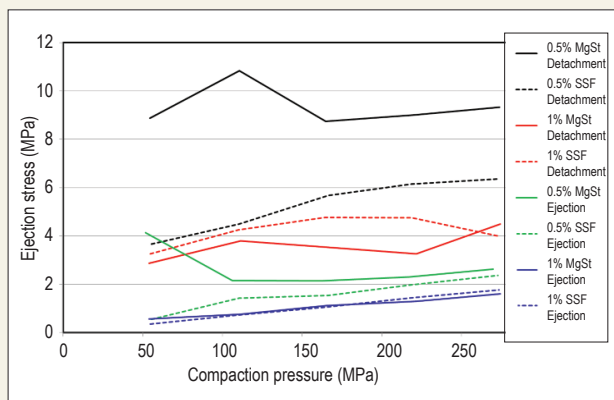
In some cases, the more popular magnesium stearate was the better lubricant, and in others sodium stearyl fumarate was clearly more effective and the better choice. This type of information has, to our knowledge, never been available at the formulation stage. Yet it is a vital element in selecting the most appropriate formulation because poor formulation choices often translate into products of suboptimal quality. They also contribute to ongoing and costly manufacturing problems throughout the product's lifecycle.

FIGURE 4

Effect of lubricants on tablets made from Pearlitol 500DC mannitol and Galen IQ720 isomalt



a. Tensile fracture stress of Pearlitol 500DC and Galen IQ720 tablets



b. Detachment and ejection stresses of Pearlitol 500DC tablets

Continuous improvement

Improving processes that have already been developed and transferred into manufacturing is a serious challenge, despite the FDA's guidances on scaleup, and post-approval changes, known as SUPAC. In fact, the guidances prevent all but the most minor changes to the formula without prior approval, and getting permission for even a minor change can take years.

Furthermore, replacing a material with one that meets the same specification as what was cited in the NDA or ANDA is prohibited. Indeed, the new FDA vision, presented in "Guidance for Industry: Process Validation Guidance: General Principles and Practices" [11] states:

Data gathered during [the third validation] stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented.

However, the guidance continues, "Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted." An associated footnote further states, "Certain manufacturing changes may call for formal notification to the Agency before implementation."

In reality, the SUPAC guidances do not address minor process changes within the operation of currently used equipment. It would be interesting to hear the FDA's view on that. Furthermore, it would be helpful if minor processing changes could be accepted by the FDA after they have undergone proper risk assessment and vetting by a company's quality management experts.

Outside the USA, manufacturers may have more latitude; it depends on what they stated in the regulatory dossiers. But in general, outside the USA, actual batch manufacturing documents are not submitted to regulatory authorities, and minor changes to processes, so long as they are geared toward optimizing quality, are more acceptable. Thus improvements linked to grade substitutions or adjustments to operating conditions of the current equipment are less likely to concern regulators. Laboratory testing that evaluates process changes on small-scale equipment is also more likely to be accepted and have in fact been used to substantially improve yields and reduce batch failures.

Conclusion

More manufacturers are turning to lab-scale and at-line compression and fracture testing instruments to implement a continuous QbD approach to tablet development. We can thus look forward to significant improvements in tablet properties as these small-scale experiments identify better excipients and processes. This, in turn, will improve consistency and yield while reducing batch failures and costs, which are all benefits that ultimately accrue to patients.

As an industry, our goal should be to convince the FDA to allow minor processing changes or grade substitutions within a pharmacopoeial specification. Such changes are in the best interests of both pharmaceutical manufacturers and patients because they improve existing products and reduce batch failures. In short, the FDA should give us the opportunity to implement a science-based, QbD approach to tablet development using technology that contributes to a common goal: making better tablets.

T&C

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Michael Gamlen, PhD, is managing director of Gamlen Tableting, Biocity Nottingham, Nottingham NG4 4GF United Kingdom. Tel. +44 115 912 4271. Website: www.gamlen-tableting.com. He has more than 30 years' experience in tablet development and led tablet development at The Wellcome Foundation for 15 years. He specializes in managing product development, formulation, and tablet and process development studies. Joe Domingue is president of SciMark International, Laguna Niguel, CA. Tel. 949 495 7795. E-mail: joe.domingue@gmail.com. SciMark is the North American representative of Gamlen Tableting.