

The Future of Compaction Pharmaceutical Tableting in the Twenty-First Century

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Currently, high-production rates and continuous production processes favor existing tableting technologies. However, if tablet development becomes rate-limiting in the future, alternative technologies may prove attractive.



Figure 1: The three-dimensional architecture of the Aprecia 3DP tableting system.

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Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipient and equipment choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in drug discovery such as genomics. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format given the difficulty of dosing such moieties orally.

Injections generally are not favored for use by patients unless facilitated by sophisticated autoinjectors such as the one used with GlaxoSmithKline's sumatriptan migraine treatment. Inhalation is one alternative, but chitosan-enhanced protein/peptide delivery has led to a rise in nasal delivery products such as the ChySys system (West Pharmaceutical Services, Lionville, PA). However, the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights, and at the same time, the development of enhanced oral protein delivery technologies continues to advance.

Modern rotary tablet machines look more sophisticated and have more instrumentation today, but the basic technology has not significantly changed in several decades. Tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for the simplest direct compression processes. Wet and dry granulation methods add further complexity to the manufacturing process. Compaction simulators, process analytical technologies (PAT), and advanced computational techniques increasingly are used to minimize this tableting black box (1), but fundamental predictability remains elusive (2).

Compaction simulators

Compaction simulators are generally single-punch compaction machines under computer-controlled hydraulic actuation to simulate other tablet machine geometries and speeds. A novel alternative is the “Prester” model (Metropolitan Computing Corporation, East Hanover, NJ), in which a tooling assembly is fired on a rail through a single set of compaction rollers (a linear analogue of the rotary turntable). Compaction simulators are becoming more common, not just within the major pharmaceutical companies but also among tableting excipient suppliers, to maintain consistency, assist tablet development, and troubleshoot problems. Equality of compaction profile does not rule out other excipi-

ent differences that may be significant in terms of tablet production.

Modern rotary machines are capable of production rates in excess of a million tablets per hour, which can be boosted, using multiple tools per die, to the tens of million tablets per hour. However, such outputs are the exception rather than the rule because of the small-volume batch-centered approach of the pharmaceutical industry, both for preliminary blending or granulation and subsequent film coating. It is not feasible to optimize every new tablet formulation for high-speed production, because most formulations do not make it through to market. Second-generation production-optimized formulations and processes can be developed later but are subject to regulatory and validation constraints that tend to discourage such improvements.

Enhancements to tableting technology include ultrasound during tableting to improve compactability (3–5) and a novel centrifugally fed tablet machine (IMA, Bologna, Italy). Contrary to expectation, the latter did not improve powder flow to the dies (6), which may explain the limited adoption of the most radical tablet machine redesign in recent years.

Improving tableting with PAT

The use of PAT is another approach to improving manufacturing processes such as tableting. PAT is a general term covering the application to drug manufacturing of process analytical chemistry tools, feedback process controls, information management, and product/process optimization. The implementation of

these technologies involves the on-line measurement of quality and performance together with multivariate statistical and pattern recognition methods. PAT has been strongly advocated by FDA to encourage innovation and improvement in an industry in which manufacturing processes have long been recognized as relatively inefficient. The conventional approach of testing quality after each stage of manufacturing, to allow progression to the next stage, means that tablets typically spend more time awaiting release than it takes to manufacture them. PAT attempts to drive intrinsic quality using nonparametric release, which is a challenge for tableting given the dependence on destructive test methods (disintegration, dissolution, and hardness) that do not lend themselves to on-line testing. A good example of a PAT method is nondestructive tablet hardness testing using near infrared (NIR) spectroscopy (7). PAT may pose challenges to some tableting processes, however, if the insight gained is not matched by commensurate process control. Closer scrutiny could reveal variations in existing products missed by current sampling and testing. Although a grace period for reducing or eliminating such variations may be allowed, regulatory authorities will expect the industry to improve manufacturing processes.

New technologies

New technologies exist that do not yet match current tableting production output rates, but these alternatives could be more attractive in the future if the art of tablet development be-

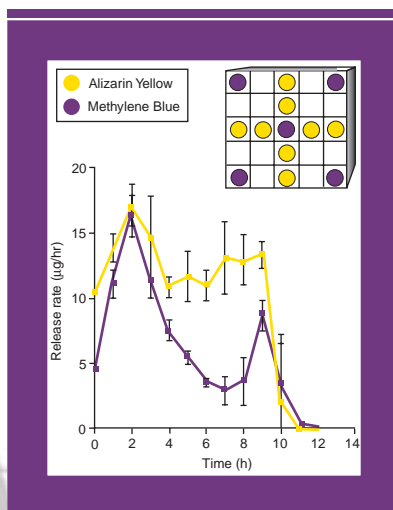


Figure 2: Spatial release control is achieved in the Aprecia system by an asymmetric distribution of drug within identical walls. This example shows a test conducted with marker dyes (adapted from Reference 8).

comes rate limiting or if drugs in general become sufficiently potent to challenge the content uniformity limits of existing tableting technologies. These newer technologies afford greater scope for validation and control and are relatively free from scale-up problems—the few units produced for early clinical trials will be identical to production units, with scale-up in output only a matter of equipment multiplication.

One example of a new technology is the “Delsys AccuDep System” (Sarnoff Corporation, Princeton, NJ), which uses electrostatic deposition of pure drug substance onto a film substrate. Dosing is controlled by applying an electrostatic charge to spots on the film so that a cloud of oppositely charged drug particles deposits the target dose at point-of-charge neutralization. The drug-

loaded film is laminated to seal the deposited doses, which can then be punched out and encapsulated or embedded in a tablet. The deposition process itself is excipient-free, but edible films are required as a substrate, and conventional excipients would be used for subsequent encapsulation or embedding in a tablet. The low levels of drug loading that are possible with this method make it best-suited for potent compounds.

The "LeQtrados" (Phoqus, Kent, UK) process uses electrostatic dry powder coating of conventional tablets to provide visually distinct coated tablets, but the coating could also be used to precision-load placebo tablets with low drug doses, provided the drug is not affected by the hot annealing process used to seal and bond the deposited powder coatings onto the tablet. The film formers must be electrostatically chargeable and thermally annealable.

"Three Dimensional Printing" (Aprecia Pharmaceuticals, Langhorne, PA, under license from the Massachusetts Institute of Technology) uses the precision of ink-jet printing with multiple print layers to build three-dimensional constructs in which the loading and spatial distribution of a drug is precisely controlled, together with a similar control of barrier materials to modify release in a programmable manner (8) (see Figures 1 and 2). Diffusion path lengths, the diffusivity of the polymers used, the thickness of the diffusion barriers, and the number of barriers can be varied. This system offers wide latitude in drug loading and excipient choice.

Conclusion

Existing tableting technologies are well suited for high production rates and continuous production applications. However, if increased tablet formulation throughput (and the associated skills) prove rate limiting, the new technologies may potentially be attractive, because they are more amenable to scale-up, validation and the PAT-driven shift to nonparametric release.

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