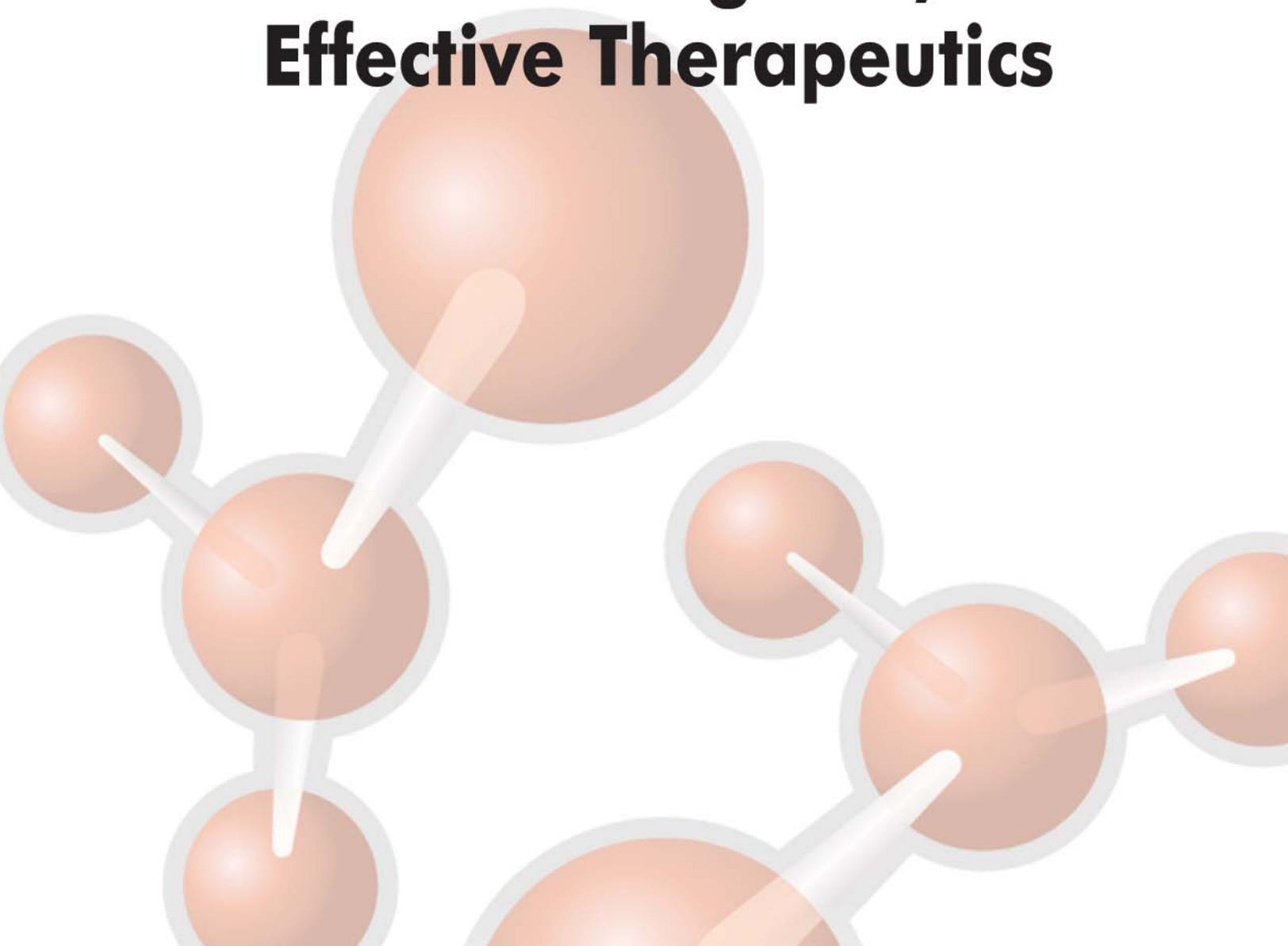


Microtableting: Going Small To Create More Targeted, Effective Therapeutics



By Matt Greene, Formulations Scientist, CoreRx

The desire to create more targeted, effective therapeutics with fewer side effects has driven drug formulators to expand into more technically demanding areas over the past decade. Microtablets are one result of this burst of creativity and engineering expertise. Going small opens up numerous new delivery options, but also creates additional challenges for drug formulators and manufacturers.

Microtablets — which are typically defined as being smaller than 5mm in diameter — enable therapeutic options that are very difficult or impossible to achieve using other delivery formats. The size is the key differentiator. Tablets that are just a few millimeters in diameter have a much greater surface area to volume ratio than standard oral dosage forms. As such, tiny tablets can have a radically different dissolution profile.

Whereas a standard tablet may break down slowly as it passes through the gastrointestinal (GI) tract, a microtablet undergoes rapid particle dissolution. Complete release of the API within 10 minutes is achievable. When combined with a formulation that only breaks down when exposed to pH levels found after a certain point in the GI tract, the abbreviated release window of microtablets allows drug developers to deliver high therapeutic loads to very specific areas of the digestive system.

Microtablets can also be used for multiparticulate dosage forms, either to deliver several different APIs or one drug

with multiple release profiles. This is achieved by filling a capsule with multiple microtablets that have different dissolution profiles or APIs. If a company decides to adjust the proportion of the different APIs or release profiles during the development, formulators just have to adjust the mix inside the capsule. Subsequent generic manufacturers would face a tricky reformulation.

Alternative routes to multiparticulate dosage forms have other disadvantages, too. The use of extrusion/spheronization or rotary granulation, for example, are undermined by the difficulty of getting the controlled-release polymers to form spheres. Release modulation from such particles is typically achieved by subsequent coating operations where controlled-release polymers are layered onto the surface of the particles. Microtablets allow for the utilization of more traditional controlled-release technologies where release modifying excipients are incorporated into the tablet matrix. Coatings may be applied to microtablets to further modulate the release profile, but are not required as with other means of multiparticulate preparation.

Microtablets are a convenient platform for other drug delivery needs as well. In early, pre-clinical development, microtablets are well suited for use in animal model toxicology and pharmacokinetic studies. Their small size makes them more easily administered to the animals at strengths which are appropriate for the



animal's body weight. In early PK studies, microtablets offer a means of evaluating tablet formulation performance as the drug release is more easily modulated from microtablets than from more commonly used pre-clinical dosage forms such as API in a capsule or suspension for gavage. Microtablets' small size also makes them a suitable depot for API in implantable devices. The tablets can be made at sizes that would allow for their insertion into the bore of urethane or silicon tubing which can be further modified to implant in the body for very prolonged delivery of the active compound. Microtablets may also be used as an alternative to multi-layer tablet systems. Inclusion of microtablets in a powder blend for tableting can allow for incompatible APIs to be compressed together or for the generation of different release profiles from a monolayer tablet. Including multiple APIs in a single dosage form can create stability problems, and raises the risk of dose dumping if the release coatings or polymer matrices fail. The microtablet approach of multiple, separate tablets in one dosage form makes stability and dose dumping less of a concern.

Assessing The Pitfalls Of Microtablet Production

Microtablets offer other benefits to formulators — such as the ability to deliver high concentrations of APIs — but also create their own set of challenges. Again, many of these difficulties relate to the size of the tablets. Small, lightweight tablets are liable to become stuck by static forces when passing through a standard feeder system. Manufacturers must

use special vibratory feed systems and static mitigation techniques to prevent blockages.

Uniformity is also an issue. The small weights of APIs involved mean there is no margin for error. Even a small difference in the amount of active ingredients from tablet to tablet can translate into a significant variation in percentage terms. To uniformly fill 2mm dies, the materials must have excellent flow properties. This almost necessitates the use of granulations with very tight particle size distribution and flow property specifications.

Operating at such small scales also affects tablet punches. A punch for a 2mm tablet is by necessity very delicate. To compensate for this inherent weakness, equipment manufacturers have developed punches that feature multiple tips. These designs reinforce the rigidity of the punch and cut the risk of equipment failure as well as increase product output. When combined with a tablet press cam design that limits the travel of the punch, used by a skilled operator, such equipment is as effective and reliable as full-sized tools.

Once a microtablet has been dosed, compressed, and moved along the feed, it comes to the final hurdle: Quality control. Visible measurements are harder to make when working with microtablets than normal sized drug products. The process requires more dexterous operators — forceps are often used to manipulate microtablets — and special equipment. Microtablet-tailored machinery is



particularly important for measuring physical properties such as hardness, a process that can be impossible without dedicated tools.

Picking The Perfect Microtableting Operation

When establishing an in-house microtableting operation or choosing a third-party manufacturer with which to work, it is important to consider all of the aforementioned challenges. Microtablets are just small tablets, but in this instance size really matters. Production steps that are simple when working with full-sized tablets can be very demanding when the products are scaled down to just a few millimeters in diameter.

The best microtableting sites combine the dedicated equipment needed to compress, coat, and process the products

with manufacturing line workers who have the skills to operate at such small scales. Ideally, such an operation will possess the ability to take a microtablet from early-stage development through to late-phase clinical supply production. Working with such an integrated, end-to-end development and production team cuts the risk of encountering problems when scaling up manufacturing.

Companies that acquire access to such capabilities are well placed to reap the benefits offered by microtablets. The ability to target specific areas of the GI tract, easily combine multiple APIs, and achieve complex release profiles make microtablets an attractive dosage form for developers of new molecules and improvers of existing products across a wide range of therapeutic areas.



CoreRx, Inc.
14205 Myerlake Circle
Clearwater, FL 33760 USA
(727) 259-6950
corerxpharma.com

