A Review of Controlled-Release Technology to Improve Formulation Effectiveness

As pharmaceutical companies aim to develop “smarter” and more effective drug products with challenging compounds, formulators are turning to the latest controlled-release technologies for solutions. What are the most promising new controlled-release technologies, and what’s next on the horizon? To learn more, Pharmaceutical Technology spoke with Thomas Dürig, PhD, the senior director of pharmaceutical research and development at Ashland, about some recent advances in controlled-release technology.

Pharmaceutical Technology: What challenges do today's formulators face due to the complexity of current APIs and dosage regimens?

Dürig: Oral modified-release dosage forms have really come a long way in the last 40 years. Today's scientists increasingly face physical-chemical constraints such as poor bioavailability due to low solubility. Other times, they need to deliver very high doses of highly soluble drugs, making tablet size dimensions difficult.

For instance, the increased number of BCS Category II compounds with very low solubility presents an interesting challenge for controlled-release formulations. In this scenario, scientists need to incorporate both solubilization technologies like amorphous dispersions as well as a rate-controlling technology. This task is especially challenging with larger doses, such as those greater than 250 mg. The amount of enabling excipients in this kind of formulation is typically quite large—up to 75% of the total dosage form. Such formulations require large tablet sizes, which make swallowability a challenge for younger and older patients, especially.

A similar, though opposite, challenge occurs when you need to formulate large doses of very highly soluble APIs in controlled-release formulations. Here, the challenge is usually to sufficiently decrease the dissolution rate to achieve enough retardation without adding excessively large amounts of release- or rate-controlling polymers, which would again make the tablet difficult to swallow. The many different types of controlled-release metformin combination products on the market are good examples of such challenges.

An additional challenge is the gradual increase in what are known as BCS Class III and IV compounds with poor permeability in discovery programs. These compounds often have region-specific absorption, meaning API absorption only occurs in very specific regions of the gastrointestinal tract. To achieve controlled-release delivery, one needs to employ gastro-resident technologies, many of which are fraught with problems.

Last, in recent years, there has been an increase in combination drug products. They also pose challenges in modified-release manufacturing complexity and sometimes also require differing release rates all to be accommodated in the same dosage form.
Pharmaceutical Technology: Can you tell me about some of the latest controlled-release technologies?

Dürig: In some ways, the oral controlled-release technologies employed commercially today are quite mature and have evolved since the 1960s, primarily in the oral technologies space. Polymeric matrix tablets, coated multi-particulates, and oral osmotic pump tablets are all in use today.

Nonetheless, many innovative approaches to these traditional technologies are still being developed. For example, the inclusion of solubilized drug in the form of amorphous dispersions is one innovation on which several groups (including our Ashland R&D group) have published studies in the International Journal of Pharmaceutical Sciences. In addition, the development of optimized direct-compression grades of polymers such as HPMC (e.g., Benecel™ K100M DC) enable the avoidance of wet granulation in the manufacture of controlled-release technologies.

Another recent technology is the evolution of 3D printing for use in modified-release device manufacturing. 3D printing offers many possibilities to engineer drug delivery devices of more complex geometries, which allows the inclusion of multiple drugs and very customized release profiles.

There are also many new multilayer technologies for tablet dosage forms in the modified release and controlled space. For instance, Orexigen Therapeutics Inc. recently introduced a multilayer extended-release tablet with two drug layers separated by a disintegrating central core. Shortly after swallowing the tablet, the layers separate into two extended-release tablets: one containing naltrexone, and the other containing bupropion, which then go their separate ways in the GI tract.

Pharmaceutical Technology: What impact has the need for more efficient manufacturing processes had on modified release formulation?

Dürig: The drivers of reducing cost and manufacturing complexity, increasing manufacturing efficiency, while at the same time increasing supply chain flexibility has also made its inroads in controlled-release technologies. One of the first things that comes to mind in this area would be the keen interest in continuous processing, which has significant advantages in terms of batch size, flexibility, and efficiency in development and scale-up.

This has led to a significant increased interest in technologies such as twin-screw extrusion for the continuous production of melt and wet granulated controlled-release dosage forms. Polymers such as hydroxypropyl cellulose are especially useful for this. An example would be Klucel™ HXF HPC, which has been applied in melt extrusion controlled-release applications.

It’s also led to a renewed focus on direct compression technologies, which are being applied at increasingly higher tableting speeds and commercial manufacturing. This places a lot of demands on optimized formulations and also selecting excipients with optimal controlled release and optimal flow and compaction properties. Ashland’s high-performance HPMC grades like Benecel™ K100M XR and K100M DC are good examples.

Pharmaceutical Technology: What do you see on the horizon for new technologies for controlled-release formulations?

Dürig: In the near term to midterm, I believe the current trend toward improved controlled release polymers and excipients will continue to keep pace with demands from more and more efficient manufacturing technologies such as continuous manufacturing melt extrusion.

Here at Ashland, for instance, we are constantly developing new controlled-release polymer technologies. There will also be an increased emphasis on developing patient-friendly controlled-release technologies, specifically for the pediatric and geriatric patient populations. Further on the horizon, we should expect increasingly large efforts to be made in the development of modified- and controlled-release technologies that allow gastrointestinal delivery of peptides and proteins.

The move toward digital medicine and the confluence of devices and drug products also presents interesting opportunities for digitally controlled or digitally interacting tablet-like drug delivery devices.