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Optimizing Semisolid Dosage Forms

Quality by design, in-vitro release testing, and modern analytical methods are improving understanding and control of these complex formulations.

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Years ago, when excipients were called “fillers” or “inactive ingredients,” drug-product quality testing was simple. The traditional approach, however, often sets the stage for process variability and manufacturing and quality problems.

Today, more is known about the potential interactions that can occur between excipients and active ingredients, as well as the impact of raw-material variability on the final drug-product quality. Quality assurance is evolving to a multidisciplinary approach that requires an understanding of materials properties on the molecular and physical level, and of critical quality attributes (CQAs) and potential product failure modes.

Taking a quality-by-design (QbD) approach can be difficult when dealing with semisolid dosage forms because of their complex flow behavior. Some semisolids can act like a liquid and a solid within the same formulation at different times and under different conditions.

Another problem is the fact that every formulation is different, says Alyn McNaughton, director of analytical and product development, Encap Drug Delivery, a division of Capsugel Dosage Form Solutions. “Excipients are used functionally to achieve different objectives, including bioavailability enhancement, dose homogeneity for low-dose drugs, high-potency safety, and abuse resistance. As such, each product must be considered individually within the lens of its specific function and desired outcome.”

A simple “cream” may contain several excipients, solubility enhancers, and partially dissolved API, and may distribute the drug in a potentially complex or dynamic way. Sameersingh (Sam) Raney, scientific lead for topical and transdermal drug products at FDA’s Office of Generic Drugs, and former professor of pharmaceutics at the North Dakota State University, reminded attendees of the challenges at a special session on October 2015, at the 2015 American Association of Pharmaceutical Scientists’ (AAPS) meeting in Orlando, FL (1). Given the complexity of creams, he said, several different attributes may be crucial to product quality, and several failure modes may be possible. Approaches will need to take multiple factors into account. Excipient selection can have a significant impact on performance attributes, as Norman Richardson, global development and technical marketing manager for BASF Pharma Ingredients Services, explained at the meeting. Research is under way to help clarify some of these issues. This article reviews some of the work going on in this area.

Traditional testing cannot address variability

Traditional quality testing for semisolid dosage forms typically focuses on viscosity, the effects of changes in temperature, and flow. Although these test methods may be indispensible, when used alone, they are not sufficient in examining potential for variability, says Kuljit Bhatia, vice-president of research and development at DPT Labs and a North Dakota State alumnus. “These compounds contain emulsions, composed of an oil phase and a water phase, with surfactants and emulsifiers. We keep all these ingredients together on a shelf for two years during stability testing, but how can we ensure they are stable?” he asks.

Test selection usually depends on the target product profile (TPP) of the dosage form and the formulation composition, explains McNaughton. For example, pH-stat digestion testing is typically used to quantify solubility improvement for lipidic bioavailability-enhancement projects, while x-ray powder diffraction and differential scanning calorimetry are usually applied to characterize amorphous dispersion and crystalline suspensions, he says.

DPT scientists are focusing on microstructure, Bhatia says, which is directly related to factors and conditions on the manufacturing floor. Understanding microstructure allows processes to be optimized, according to Bhatia.

Scientists use microscopy and laser diffraction to analyze microstructure, and then take mechanical measurements using a micelle counter (typically, a Clemex image analyzer or laser diffraction device attached to a computer).

In addition, rheology, which observes how stress affects product flow, is being used to study the compounds. Plotting sheer stress vs. sheer rate results in a curve that can be used to help predict product behavior under different conditions, Bhatia says.

“We are taking a step-by-step process to examine emulsification, chemical stress, mechanical stress, process development, and other factors including cooling and the impact of changes in temperature,” Bhatia says. One goal, he adds, is to ensure that laboratory materials are the same as scale-up materials and that such factors as globule and micelle size are uniform from batch to batch.

Michael Lowenborg, DPT Labs’ senior manager of R&D formulation and process development, explained the “microstructure” approach to studying emulsions at the AAPS session (2), and gave an example of how this approach was used to optimize the formulation and process development for an emulsion, working back from results in the lab to process design and equipment selection. Part of the work involved optimizing the hydrophobic lipophobic balance (HLB) and mixing and temperature of emulsification.

Applying design-of-experiments (DOE) and scale-up studies offers insights into the critical process parameters (CPPs) and CQAs at each process phase. Future work, he said, will focus on how variation in microstructure can affect nonphysical attributes such as *in-vitro* release.

Capsugel is also applying QbD principles to semisolid dosage forms, from the very start of the design process through to clinical and commercial manufacture, says McNaughton. “The understanding and control of CQAs and CPPs, from the concept stages of dosage form design, helps minimize any impact of manufacturing later in the process,” he explains. “It is important to determine both the tolerances of formulation and excipient ratios and combinations and the processing parameters used during manufacture at a small scale, and how these factors can change during scale up. It is also critical to know the performance and limitations of the excipients and materials that are being used, particularly those that are functional,” he says.

The fact that two companies that support contract development and manufacturing work are using more modern quality tools reflects a change in thinking within the industry. “The use of QbD has gone mainstream in the past five years, and led to a ‘debunking’ of the traditional process for semisolid dosage form development,” says Bhatia.

At the same time, more manufacturers are now using *in-vitro* release testing (IVRT) for semisolid dosage form manufacturing. A few years ago, the method was used only in some research projects, Bhatia says, but it, too, has gone mainstream, and more companies are even using it to submit new drug applications (NDAs). Two years ago, the United States Pharmacopeia (USP) published an entire chapter on the method (3), aligned with FDA guidance from 1997 (4). The goal was to standardize testing equipment and procedures.

Addressing unpredictable changes

In-vitro testing provides the only practical means of demonstrating shelf life and identifying potential changes in product attributes from unpredicted sources such as raw materials change or manufacturing impacts, explains McNaughton. “As we develop a greater understanding through the characterization of both materials and processes,

it is likely that the QbD process will allow for a more relaxed approach to standard *in-vitro* stability testing,” he says. “However, the development of more sophisticated dosage forms could also result in an increase of more specialized testing until we develop an understanding of their performance characteristics.”

Whatever directions this work may take in the future, the industry requires a new approach to semisolid dosage form development, and to staffing and training, Bhatia says.

“FDA asks for specifics on rate of release to control processes and reduced variability batch to batch, requiring a clear understanding of rate of release, risk assessment, CQAs, and the design space,” he adds, noting that his company tends to hire mainly PhDs in formulation, but also more professionals with advanced semisolids experience using rheology and IVRT.

A Simple Model for a Complex Process

Unlike homogeneous systems, where final product attributes depend solely on quantitative and qualitative attributes, creams, ointments, and gels are heterogeneous, and depend on additional factors such as temperature, the order in which ingredients are added, shear, packaging conditions, excipient source and grade, and storage time, explains Norman Richardson, global development and technical marketing manager at BASF Pharma Ingredients Services. Tests have been done on simple ointment systems containing two different polyethylene glycols and solvent to better understand issues (1). The best sensory properties were achieved by balancing fluid, gel, and solid states. When the molecular weight of one of the glycols was varied, and the ointment structure studied under cross-polar microscopy, bright regions showed less crystalline areas. Rheological studies then revealed the impact of viscosity and shear thinning. In studies of product stability, the amount of one of the glycols was varied and evaluated with cross-polar microscopy. At 5%, fluid weeping occurred immediately. At 20%, it took seven days. Formulations with 25–30% of the glycol were found to be the most stable.

Reference

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“Multi-disciplinary teams are a key component of our formulation approach to customer projects, regardless of problem statement, TPP, or finished product presentation,” says McNaughton. Such teams are mainly comprised of fundamental scientists, including materials scientists. They often complement customers’ teams, which are generally applied science-focused, he says.

While both companies recommend a QbD approach to clients as a matter of course, more pharmaceutical sponsors are proactively demanding that QbD methods be used for their projects. As a result, convergence is being seen between name-brand and generic-drug sponsors, Bhatia says. “NDA clients tend to ask for QbD explicitly, while generic-drug manufacturers may not ask for it at first,” he explains. “Given FDA’s mandate to use question-based review (QbR), however, more companies see they are going to need QbD-type data anyway, so they realize they will need to use newer methods to evaluate their products and processes.”

Modular PAT approaches likely in the future

The future may see the application of process analytical technology (PAT) more

routinely in semisolid formulations development labs. Typically, the approach is used for larger batches and continuous processing, but there may be a need for built-in endpoints (e.g., micelle size changes) that can ensure the best microstructure to ensure rate of release in the lab, says Bhatia. “PAT would allow R&D teams to build in that endpoint,” he says.

R&D groups are already developing probes and taking samples and measurements at the plant. “Evaluated on a case-by-case basis, PAT would be the logical next step,” Bhatia says. PAT approaches can be used to characterize materials and processes during development and control materials and processes during manufacturing, and can result in a reduction in in-process testing while helping reduce finished product testing, says McNaughton, noting that PAT can be used at various stages in the manufacture of semisolid dosage forms, including raw material identification testing using near infrared (NIR); assay and homogeneity evaluation; and particle-size measurement or performance testing during milling of dry powders or in suspension.

Currently, he says, these testing approaches are usually best-suited for dedicated product equipment, where they can target specific CQAs required for a particular product. As PAT system designs become more modular, he says, they will likely become standard for many areas within a manufacturing process. While not quite the same approach, similar

techniques can also be applied to characterize performance attributes during formulation development, he says. Examples would be dissolution rates and concentrations, where solubility-dependent absorption is being improved through formulation development. This would allow more rapid product development, he says, and improve the potential for success through increased in-vitro screening.

USP plans to launch a collaborative study that will involve equipment vendors, contract laboratories, and pharmaceutical companies that have expertise on the performance tests for semisolid dosage forms. The goal is to gain a better understanding of possible sources of variability when running these tests, and to better describe the test conditions in the USP General Chapter 1724, Semisolid Drug Products—Performance Tests (4), says Margareth R. C. Marques, principal scientific liaison, US Pharmacopeial Convention’s Science Division, Chemical Medicines General Chapters.

FDA is funding a number of research projects focused on semisolid dosage form measurement and assessment. DPT is working on some research that is funded by FDA under the Generic Drug User Fee Amendment of 2012 (GDUFA). FDA is also funding research by Michael Roberts and his team in Queensland, Australia, that aims to identify and define CQAs and potential failure modes for semisolid products. FDA wants to relate CQAs of drug products to *in-vitro* and *in-vivo* performance.

Research will examine the properties of APIs, excipients, and the interaction of product with the skin. The team will compare bioavailability, and use tools such as atomic force microscopy, confocal Raman, and multi-photon microscopy to study the effects of excipients and formulation *in-vitro* and *in-vivo*.

References

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3. V. Shah et al., *Topical Drug Bioavailability, Bioequivalence and Penetration*, Second Edition, p. 65, (Springer, January 2015).
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