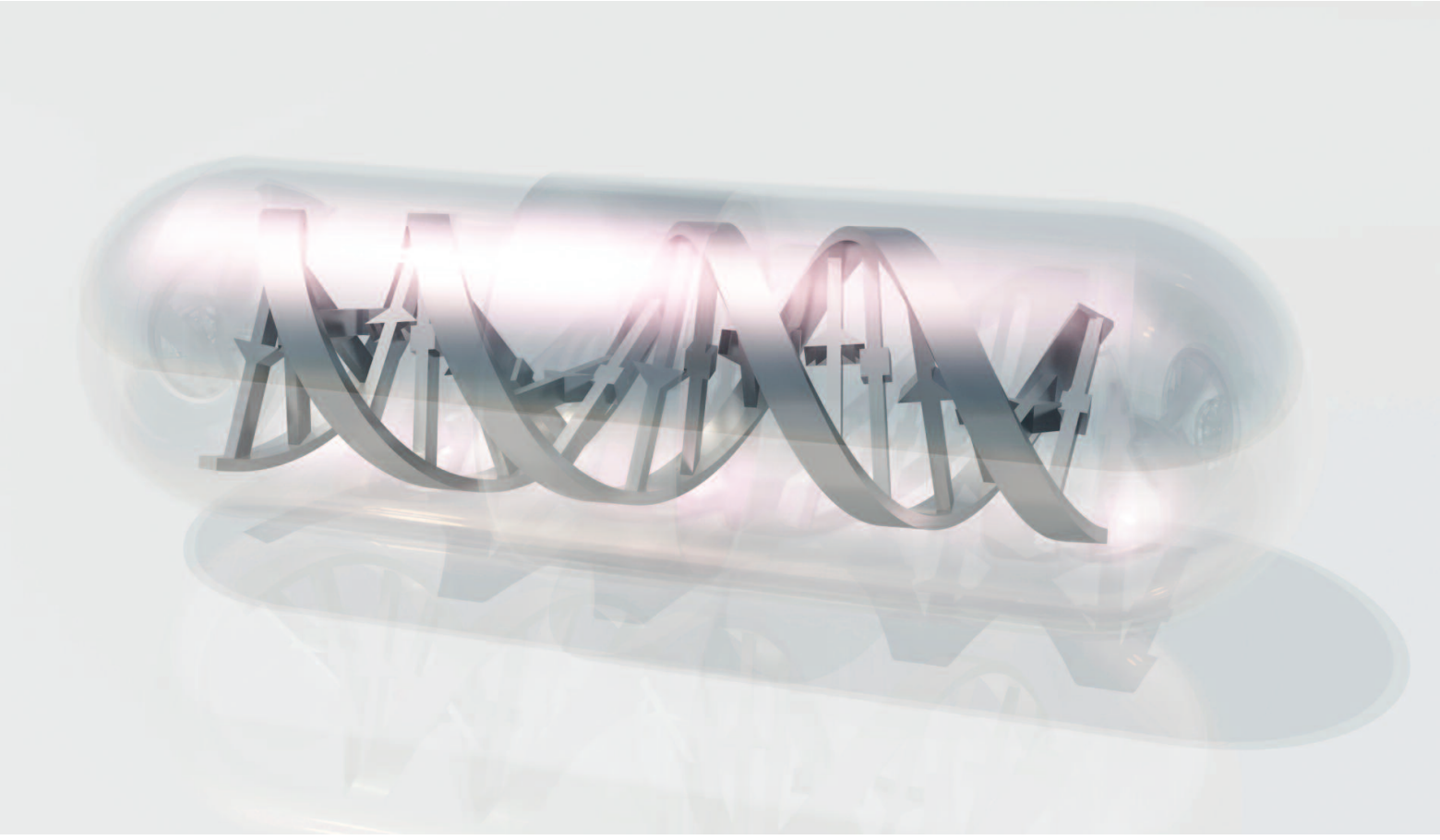


Encapsulation innovation: The new and novel in hard and soft capsules

Matthew Knopp
Editor



Judged by the number of products on the market, tablets win hands down over capsules. But capsules offer more versatility in delivering drugs and dietary supplements. Here's a glimpse at some of what's new.

No one expects capsules to overtake tablets as the preferred pharmaceutical dosage form. Nonetheless, "the capsule market is increasing by 4 to 5 percent per year in units, while the average market in units of pharmaceutical products in general is growing by 3 to 4 percent," said Martin Opitz, a senior market expert at Robert Bosch Packaging Technology, Waiblingen, Germany.

"At present, the ratio of capsules to tablets in the world is 1-to-5.5, capsules-to-tablets, and it's always a question of where the trend is going. If it's going more the capsule way, that doesn't mean we'll get close to 1-to-1, but it might become 1-to-4."

Opitz cited expiring patents as the main driver for the growth in capsules versus the market overall: As former blockbusters have lost patent protection, production of generic versions has soared. He estimated that the number of capsules used for making omeprazole went from 1 billion annually to 10 billion after the innovator's product came off patent. "There is a huge boost in volume when they become generic," he said. "Two-thirds of capsule volume is going to generics and OTCs."

That's why it's important to capture an innovator's attention at the R&D stage, he said: Whatever process, product, or technology the innovators select, the generic manufacturers will likely also adopt. That locks in future revenue from the follow-on manufacturers and "allows our capsule filling technology to stay long term," Opitz said.

That long-term relationship and the promise of bigger volumes also appeal to suppliers of capsule shells, such as Capsugel, Greenwood, SC, as well as CDMOs that formulate and manufacture softgels, such as Patheon, Durham, NC, and Catalent, Somerset, NJ.

Branching out

To capture that business, suppliers have been broadening the application of their products and expanding their offerings. Capsugel, one the largest suppliers of capsule shells, has added a number of technologies to its portfolio under its Dosage Form Solutions (DFS) business unit. In March 2013, it acquired Scotland's Encap Drug Delivery, giving it more expertise in liquid-filled lipid formulations and a commercial manufacturing facility. In October 2013, it acquired Bend Research, Bend, OR, which specializes in enhancing bioavailablity and modifying API release using spray-dried dispersions and hot-melt extrusions.

Still, capsules remain Capsugel's foundation, a fact underscored by the posters it presented at the annual meeting of the American Association of Pharmaceutical Scientists (AAPS) in San Diego, CA, in November. "We want to educate people about the advances that are taking place in capsule technology," said Missy Lowery, Capsugel's senior manager of marketing for the Americas. "It's an extremely flexible dosage form."

One example is a multi-compartment capsule under development at one of the company's R&D sites. In this variation of the capsule-in-capsule approach, one or more capsule caps are inserted into a standard capsule, enabling a single capsule to carry two or more formulations [1]. The AAPS poster presented experimental case studies that demonstrated the possible applications and concluded that the technique can be applied to combinations of all types of hard capsule polymers. "It's something that we have been developing just to see the feasibility," said Domique Cadé, Capsugel's director of polymer science. "It's part of our push to offer our ideas to the pharmaceutical industry, to see where it fits, the right application."

Photos courtesy of Capsugel

Capsugel conducted several experimental case studies of its multi-compartment capsule to demonstrate possible applications [1].

Another poster summarized a study on the performance of Capsugel's acid-resistant DRcaps capsules after being band-sealed with an ammonia-neutralized cellulosic formula [2]. In vitro tests showed the band prevented the body and cap from separating until they reached a higher pH environment. Later this year, Capsugel will begin commercial trials of the banding technology among its pharmaceutical and dietary supplement customers.

Getting capsules to the target destination was critical for Dr. Elizabeth L. Hohmann and her colleagues at Massachusetts General Hospital, Boston, MA. Their work involved transplanting donated fecal matter to the large intestines of patients suffering from clostridium difficile colitis [3]. The effectiveness of the transplantations was well established, but the first methods used—colonoscopies and intubation—were fraught with problems. Capsugel's acid-resistant HPMC capsules provided a solution. The HPMC polymer held up to the liquid fill, and the capsules' acid resistance ensured passage through the stomach intact, opening only when they reached the large intestine. Double encapsulation—a size 00 within a size 0—and deep-freezing kept the capsules intact until they were dispensed (15 capsules a day over 2 days).

Photo courtesy of Dr. Elizabeth L. Hohmann

Acid-resistant HPMC capsules give physicians a better method of transplanting fecal matter to the large intestine [3].

"Most people just close their eyes and take it right down," Hohmann said. "[The appearance] is really just an aesthetic concern because they're totally odorless and tasteless. And because they're frozen, they frost over a little bit when you get them in the air. So it doesn't matter that much." Eighteen of 20 patients were treated successfully using the capsules, and since the initial results were announced in October, Hohmann and her colleagues have treated 30 more patients with similar success.

Another study presented at the AAPS meeting compared how hard capsules made from different polymers performed in drug delivery via the vagina [4], a method that, like ocular delivery, shows promise in overcoming the blood-brain barrier. The study's authors stated that many new products that employ hard capsules for vaginal applications failed to account for the capsule's nature or functionality. Their tests, conducted using a texture analyzer, showed that pullulan capsules—Capsugel's Plantcaps—provided rapid content release through quick disintegration. The pullulan also helped keep the capsule in place through strong bio-adhesion.

Micro-dosing

Capsules also have applications in pulmonary delivery, typically in dry powder inhalers (DPIs). Capsugel presented data about how different hard capsules performed in different DPIs [5], and Qualicaps, a capsule supplier based in Whitsett, NC, offered posters that evaluated how capsule composition (HPMC versus gelatin) and temperature affected puncture performance [6-8]. [*Editor's note*: For more information about nasal and pulmonary delivery, see *Tablets & Capsules*' sister magazine *Inhalation*: www.inhalationmag.com.]

Whatever capsules are used in DPIs, it's critical that they contain the right powder dose. Until recently, that usually meant filling them using a dosator-style capsule filling machine, because tamping-style machines were not really suitable. Bosch, known best for tamping machines, will begin offering dosator-style machines this year. It has also developed a new technology, called a vacuum dosing wheel. It dispenses as little as 1 milligram of powder at a standard deviation of ±2 percent and can fill capsules with as much as 200 milligrams.

It can also micro-dose other types of powders. "We see more and more applications in dosing pure APIs and in dosing very small formulations," Opitz said. "For [fills] up to 100 milligrams, it can be very accurate, this wheel technology. It's completely different from tamping pins," he said, noting that immediate-release formulations are an appropriate application. "If you have a good soluble API, why should you go the way of formulation, where you have to test the interactions between the excipients, API, and capsule shell? Why don't you fill the API directly into the capsule? More and more, we're seeing requests from formulators who are thinking about putting just API in the final product."

Originally, filling capsules with neat API was a method to accelerate clinical trials, and one of the first micro-dosing systems to take hold was Xcelodose, a technology that Capsugel acquired in 2005. Another micro-dosing system, Quantos, was introduced in 2008 by Mettler-Toledo, Columbus, OH. Opitz, who worked at Capsugel until 2013, called the Xcelodose "fantastic," because it helps bring products to market quickly. But the dosing wheel is a better fit for scale-up and large-scale production, he said. "We improved the system so much in the last year, 2014, and it can handle a big range of different kinds of APIs or formulations in small amounts. The wheel allows you to adjust quantities, so during drug development, you can play around with different quantities by adjusting it."

Softgel science

Softgel capsules offer formulators additional flexibility. In October 2012, Patheon acquired Banner Pharmacaps, the world's second-largest pharmaceutical business dedicated to softgel formulations. "Banner gave us added value," said Anil Kane, executive director and global head of formulation sciences at Patheon. "We now can provide our clients with a softgel dosage form for delivery of immediate-release, controlled-release, as well as areas for pediatrics, geriatrics, and other special types of delivery, such as enteric-release softgels." Technologies include EnteriCare enteric-release softgels, Versatrol controlled-release softgels, Solvatrol softgels for enhanced solubility, LiquiSoft pediatric softgels, Chewels chewable forms, and twist-offs. The twist-off capsules can hold a large liquid dose, which is squeezed into the mouth. They help deliver medicine to pediatric and geriatric patients, as well as others who have difficulty swallowing tablets or capsules.

Kane said the special equipment, excipients, and expertise that softgels require aren't an issue for customers. "They prefer to outsource this to specialized groups. I don't think it's the best use of a firm's in-house skill sets to develop a small number of products in a specialized dosage like a softgel. I think it's advantageous to outsource to a specialist rather than training individuals and investing in this in-house."

It may even be faster to use a softgel instead of a liquid-filled hard capsule to get new products to market. "We can do a very small, benchtop, proof-of-concept in softgels," Kane said. "We can also take softgels from phase 1 through to later phases of development and on to commercial much faster because the vehicle is the same," he said. "So the scalability is much faster, and the output can be much higher than the two-piece liquid-filled hardshell, which needs additional steps, such as banding, sealing, and drying. We see a lot more benefits with the softgel."

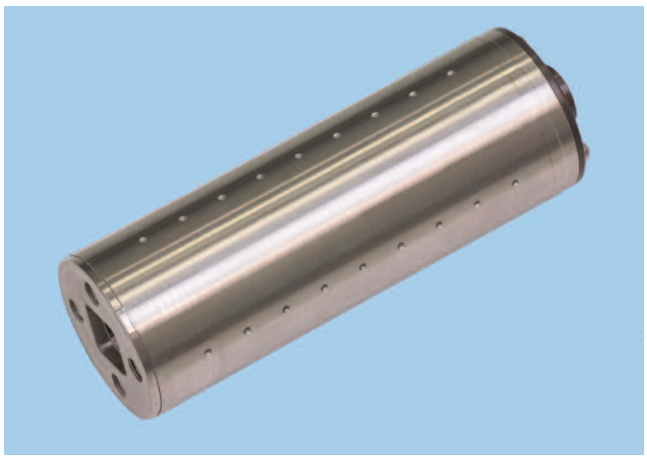


Photo courtesy of Bosch

Bosch's vacuum dosing wheel dispenses as little as 1 milligram of powder at a standard deviation of ±2 percent.

In fact, liquid-filled hard capsules have not been as popular as forecast, Opitz said. "It's a fantastic technology for insoluble APIs, and some years ago there was a big hope that a lot of products would come out, and there are some for sure. But it's not the boom that we expected at Bosch. We haven't sold that many liquid filling machines linked to the SMEDDS and SEDDS systems."

Photo courtesy of Patheon

Patheon can take softgels from proof-of-concept, through clinical trials, and on to commercial production.

Another of Patheon's technologies, Softlet gelatin enrobing, offers an alternative to over-encapsulation, the standard method of blinding clinical trial materials. "Sometimes the tablet is large and it's a challenge to fit into a blinded hard capsule," Kane said. "Actually, we are seeing more of that: fixed-dose combinations getting larger and larger, and it's a challenge to fit them in a blinded capsule, so a Softlet enrobing approach can help. It's all based on engineering, devising the tooling." Odd-shaped tablets, multiple tablets, and powder- or pellet-filled capsules can also be enrobed to blind clinical trial materials. "There is no one solution that solves all problems. Our approach is to provide the fastest and most cost-effective approach, whether it's a two-piece shell or softgel form."

Softgels can also help formulators overcome the difficulty of delivering biopharmaceuticals via the oral route. "No major breakthrough in the effective oral delivery of peptides/proteins has been accomplished," said Shinji Yamashita of Setsunan University, Osaka, Japan [9]. At the same time, there is a trend in drug development toward bio-molecules over small-molecule compounds, he said, and that has increased the demand for oral delivery of biologics, especially of therapeutic peptides and proteins.

Catalent, for one, is working on it, mainly via its OptiGel Bio technology, which aims to put proteins, peptides, and other biological molecules—normally delivered by injection—into an oral dosage form. One of

Breaking the GI barrier with micro-needles

Seven of the top 10 best-selling drug products are biologics, but none of them is delivered orally, said Shinji Yamashita of Setsunan University. "The oral delivery of biologics has attained a high level of science, but very few real-world products so far." Meanwhile, the science continues.

Researchers at the Massachusetts Institute of Technology and Massachusetts General Hospital have developed an oral capsule coated with tiny needles that injects drugs into the lining of the GI tract.

In animal studies, the capsule delivered insulin more efficiently than subcutaneous injection, and its needles had no harmful side effects. In addition to insulin, the device may be capable of delivering antibodies to treat cancer and autoimmune disorders, as well as vaccines, recombinant DNA, and RNA.

Such biologics are difficult to deliver orally because their large molecular size prevents absorption in the GI tract. But the capsule's micro-needles overcome that barrier by directly injecting the payload. Since there are no pain receptors in the GI, the injection is painless. In tests on pigs, the device injected insulin into the stomach lining, small intestine, and colon. It took more than a week for the capsule to pass through the digestive tract.

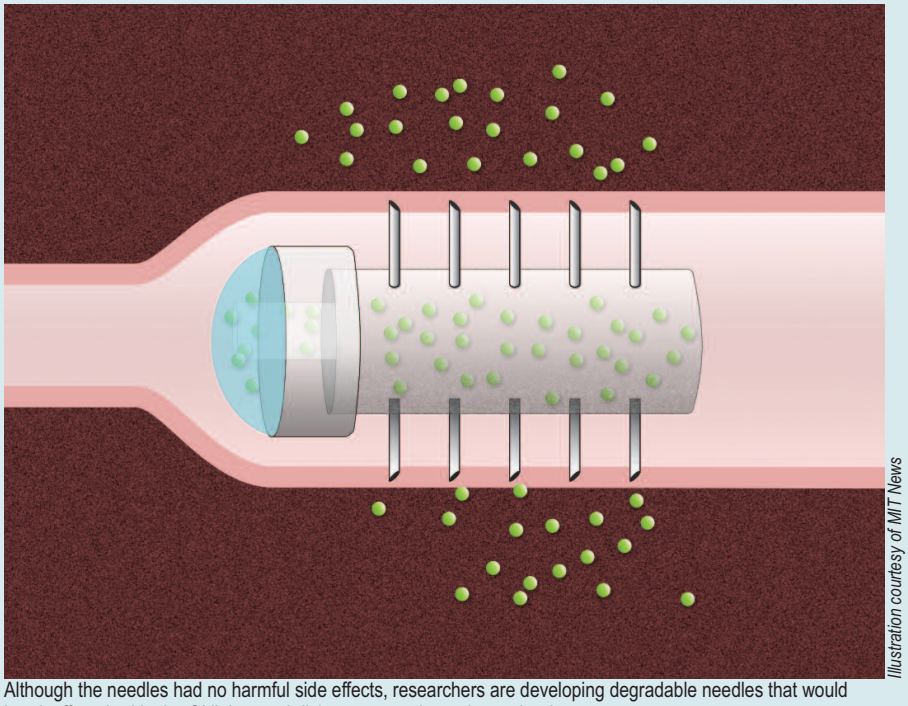


Illustration courtesy of MIT News

Although the needles had no harmful side effects, researchers are developing degradable needles that would break off, embed in the GI lining, and disintegrate as they release the drug.

Researchers are now developing a capsule with needles made of degradable polymers and sugar. They would break off, embed in the GI lining, and slowly disintegrate while releasing the drug.

A summary of the study, "Microneedles for drug delivery via the gastrointesintal tract," appeared online September 22, 2014, in the Journal of Pharmaceutical Sciences.

— M.K.

Photo courtesy of Catalent

Catalent's softgels include a variety of OptiGel technologies to deliver biopharmaceuticals orally, deter abuse, and modify release. Its OptiGel Micro softgels (bottom) are seamless and easy to swallow.

the first candidates was a very low-molecular-weight heparin, which the company studied at one of its European R&D sites. "While that is not a large-molecular-weight API, the results show the promise of our technology," said Jeff Browne, Catalent's R&D director of pharmaceutical softgels in the USA.

The technology uses enteric-coated softgels to deliver the API and permeation enhancers to the small intestine, where they open. "Once they reach the instestine, they are designed to rupture quickly after dissolution of the enteric coat, even with the minimal volume of fluid that you have in the small intestine compared to the stomach," he said. "After they rupture and the shell dissolves, the fill is released, providing a very high local concentration of API and permeation enhancers at the area of the GI where absorption can occur." The permeation enhancers, typically medium-chain free fatty acids, are released from GRAS-listed ingredients in the fill formulation via normal biological processes, thereby opening the tight junctions between the GI cells. That allows the API to enter the bloodstream and exert its therapeutic effect. "We can't say this is the answer to delivering all proteins and peptides orally, but we have the promise of a technology that has shown what it can do for several model compounds that we've taken through animal studies."

Catalent's latest offering is OptiGel Lock, an abuse-resistant technology that enables companies to comply with recent FDA guidelines for preventing abuse of opiates and other pain-management medications. "What we've shown, through in vitro data primarily, is that we have fill formulations and systems that are resistant to extraction and inhalation procedures that abusers use," Browne said. "Basically, we think [the technology] meets the major criteria to claim that we have an abuse-deterrent product" for extended- and immediate-release products. He said many pharmaceutical companies are scrambling to comply with the FDA guidelines, which in many cases will likely require them to reformulate existing products. "Whether those are tablets or hardshell capsules, we feel this softgel technology is as good or better than many of the other options on the market."

Photo courtesy of Patheon

Combination fills illustrate the flexibility of soft and hard capsules. Here multiparticulates are combined with a liquid fill in a hard capsule.

Photo courtesy of Bosch

The GKF 702 from Bosch fills capsules with tablets, powders, pellets, and liquids, either individually or in combination. For powder fills, it uses either tamping pins or dosators.

Combinations and self-dosing

As the number of high-volume blockbusters fades and pipelines dry up, pharmaceutical manufacturers are turning to new delivery methods and combination products to extend the life of their brands. Last year, Capsugel introduced a "sprinkle" version of its Coni-Snap capsules for use by patients who have difficulty swallowing. To access the fill—usually beads or multipartculates—patients pull the capsule apart and sprinkle the contents over a soft food. Catalent offers OptiGel Mini, a technology for making very small, seamless softgels. They're made at the company's site in Japan, where consumers prefer small dosage forms. Most are packaged in sachets or foil pouches, allowing consumers to add them to food and to manage the dose.

To satisfy stronger demand for combination fills, Bosch offers equipment that fills as many as three different types of materials, including powders, pellets, granules, tablets, and liquids, into a single capsule. Opitz said micro-tablets are an especially popular format. "Twenty years ago, there were a lot of new chemical entities launched, and line extensions were not a focus for Big Pharma." Today, however, as new APIs become less common, the strategy has changed. "They're now reformulating their old APIs or combining them, and since a lot of APIs are incompatible with each other they must be conveyed using a different kind of formulation."

T&C

References

1. He, Xiongwei et al. Multi-compartment hard capsule and potential applications. Poster W5133, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

2. He, Xiongwei et al. DRcaps capsules banding for improved acid resistance. Poster W5132, AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

3. Youngster, Ilan et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing clostridium difficile infection. JAMA, 2014 Nov 5;312(17): 1772-8.

4. Straub, Hugues et al. Hard capsules for vaginal applications. Poster R6248, AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

5. Tardy, Claire et al. Capsules for dry powder inhalation—Performance evaluation of different capsules with various inhalation devices. Poster T3174, AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

6. Dharap, Sonia et al. Understanding intra- and inter-individual differences in capsule puncture following actuation of a dry powder inhaler. Poster T3175, AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

7. Diez, Fernando et al. Influence of temperature on capsule puncture performance. Poster T3176, AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

8. Jones, Brian et al. The puncture properties and shedding of particles of capsules in dry powder inhalers, effect of capsule type and moisture content. Poster T3178, AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.

9. Yamashita, Shinji. Ambition or just a dream? History and future perspective for oral delivery of biologics. Presentation at AAPS Annual Meeting and Exposition, San Diego, CA, November 2-6, 2014.