SINGLE-STEP FUNCTIONAL COATINGS FOR INCREASED EFFICIENCIES

In this article about oral drug innovation, Cory Berkland, PhD, Co-Founder & Chief Scientific Officer, and Nathan Dormer, PhD, Vice-President of Research & Development, both of Orbis Biosciences, focus on how enterics and reverse enterics are applied into dosage forms, and discuss the future of this class of drug formulation technology.

Drug formulation and delivery focuses on preserving active pharmaceutical ingredient (API) function while the drug is ushered to the specific site of absorption and/or action at the right time and in the right quantities. This can be a difficult task considering the physical, chemical and biological obstacles the human body presents. The natural impediments the body presents are the primary reason so many drug delivery approaches exist.

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One of the oldest and simplest routes of administration, oral delivery, is no stranger to formulation evolution. Oral dosage forms have arguably seen the most progressive transformation, advances building on each other over time leading to innovation and invigoration of traditional pills, tablets and capsules. One of the most useful inclusions for creating next-generation oral dosage forms are pH-responsive materials, colloquially referred to as enterics and reverse enterics.

Enterics and reverse enterics, typically applied as pill or tablet coatings, are only soluble in specific pH ranges, which enables them to have site-specific gastro-intestinal release, such as the mouth, oesophagus, stomach, and specific regions of the small and large intestines. In the simplest circumstances, enterics are used either to prevent gastric mucosal irritation or to protect pH-labile APIs from degradation. Reverse enterics are primarily used to bypass the oral mucosa (for taste and odour masking), while maintaining immediate-release behaviour once reaching the stomach.

The most widely used methods for applying enteric and reverse enteric coatings involve solvating or dispersing the coating powder in an aqueous or organic species then spraying the coating solution onto the

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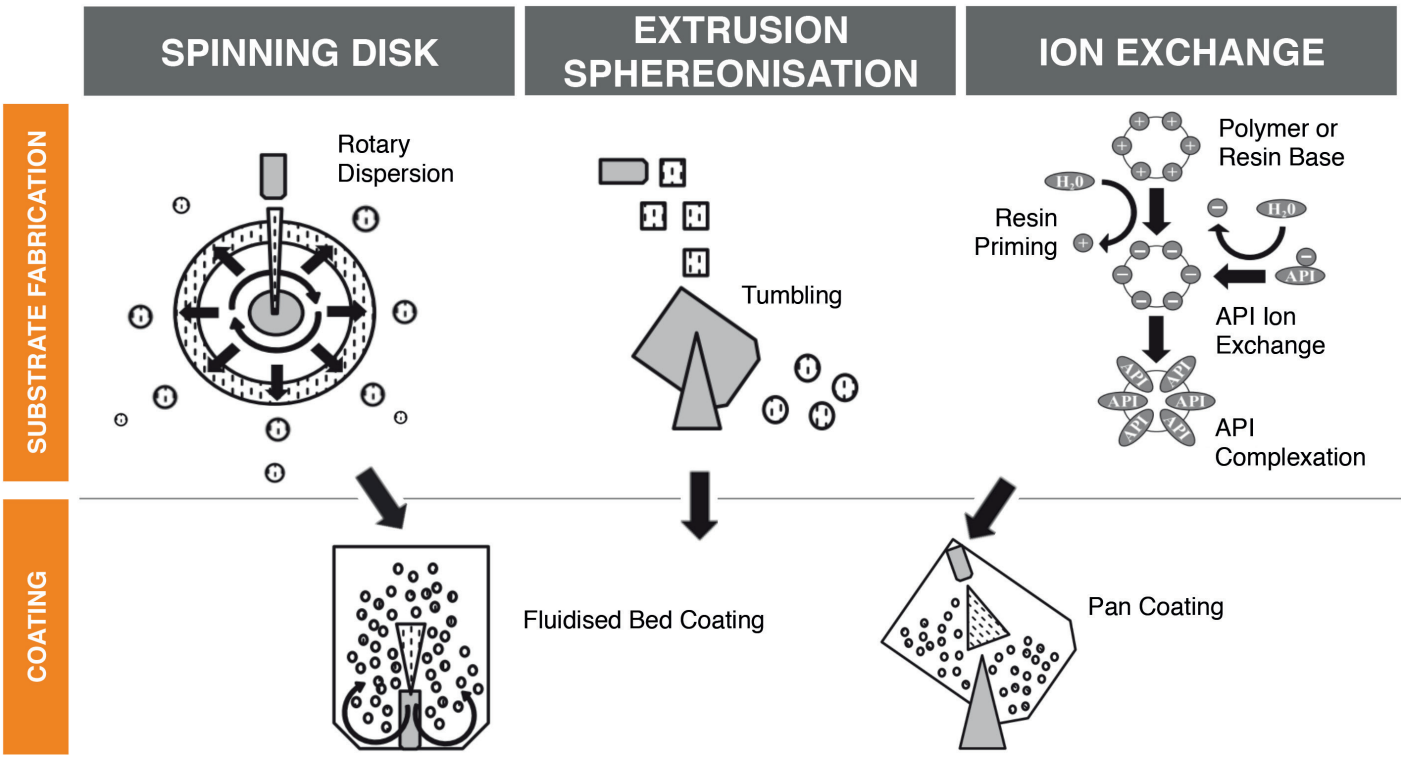

Figure 1: Coating of tablets, capsules and dispersed dosage forms begin with creation of the substrate core. Then, in a second step, enterics or reverse enterics are applied as coatings.

pill or tablet using pan coating or fluid bed coating. Notably pan coating and fluid bed coating are batch processes with multiple steps (Figure 1).

Pan coating (which in reality utilises a rotating drum) allows the tablets or substrate to tumble while an enteric or reverse enteric solution is sprayed on at a controlled rate. Newer pan coating machines have an internal drum layer that is perforated, which allows for more expedient evaporation of the coating solvent and subsequent hardening of the coating layer.

Fluid bed coating utilises a similar spray-on approach, but greatly increases the inter-tablet or inter-substrate space by using air to circulate the mini-tablets, pills, etc, and then dry them, all in the same piece of equipment. This allows very small substrates to be coated, but at the cost of using large volumes of solvent solution and subjecting the substrate to high shear stresses during circulation, which can negatively affect coating friability. Fluid bed coating, however, is relatively quick compared with pan coating.

Nonetheless, despite the theoretical simplicity of pan coating and fluidised bed coating, the processes involve extensive validation of coating thicknesses within a batch, between batches, and the general tolerances of those thicknesses in terms of product quality and reproducibility. Just one region on a tablet or pill with a thinner applied coating can compromise the intended performance of the entire dosage form. A technique to circumvent the difficulties of achieving a consistent coating is to utilise microparticles rather than one large pill. The microparticles are sieved prior to performing pan or fluid bed coating with the intent of increasing the probability of batch contents receiving an even coating. The particles are then coated with the enteric or reverse enteric and utilised as a drug product intermediate for capsules, sachets or even liquids. Although this process has a burdensome number of steps, microparticles provide superior format flexibility, taste-masking, dosing routes and the potential to circumvent food effects.

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Whether utilised for a tablet or microparticle application, enterics and reverse enterics are seldom used in a standalone manner, and are commonly applied over other materials that exhibit modified-release properties (such as extended-release polymers) or excipients that enhance solubility and/or permeability. In other instances enteric and reverse enteric coatings are used in conjunction with one another to achieve specialised release profiles for one or multiple APIs. Considering scenarios like this, one can see that traditional approaches for creating modified-release solid oral dosage forms can easily involve several batch-wise steps, compounding time, personnel and operating expenses.

In addition to the incremental cost associated with multiple coating and validation steps these processes often result in variable coating thicknesses that can affect product performance.

The most obvious fix to the burden of multiple coating steps is to create a technique that consolidates all of the necessary excipients and coatings into one manufacturing step. Specifically it is to apply the coating at the same time the tablet or pill is fabricated. Historically the physical

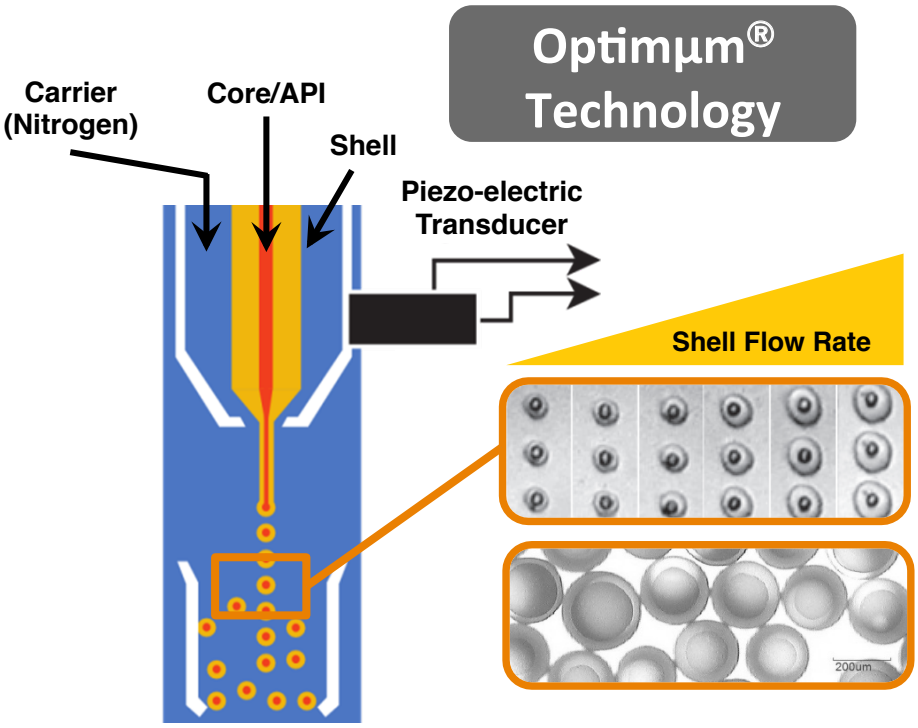

Figure 2: Orbis' Optimμm® technology can apply an enteric or reverse enteric coating over an API-rich core in a single manufacturing step, which eliminates the need for pan or fluid bed coating and provides the additional advantage of having a particulate dosage form that can be used as a stand-alone solution or integrated into other oral dosage forms, such as capsules or orally-disintegrating tablets.

ability to do this has not been available due to the coating solutions being liquid when applied and the tablet compression mechanism not allowing for application of said liquid. However, at Orbis we have developed a process to coat the substrate (with an enteric, reverse enteric or any polymeric material) simultaneously as the substrate itself is being created. Orbis' proprietary Optimμm® technology uses two liquid streams flowing through concentric nozzles to achieve a coated microsphere in a single manufacturing step.

Optimμm® technology allows processing of viscous wax, lipid, enteric and API solutions through a vibrating nozzle to make small coated microspheres ("microcapsules") which behave like tablets, all in a single step (Figure 2). Using simple process parameters, such as flowrate and frequency of vibration, Optimμm® technology can create microcapsules with various shell thicknesses and overall sizes, which enable tailoring of release profiles and high API content for such a small form factor. The ability to coat drug-loaded cores completely with enterics (Figure 3a) and reverse enterics (Figure 3b) allows Orbis' manufacturing platform to combine modified-release dosage forms with the desirable form factor of microparticulates. In addition to single-step coating, Optimμm® technology retains superior control over microsphere size distribution, enabling highly accurate and reproducible manufacturing scale, powder dosing, API release and therapeutic performance.

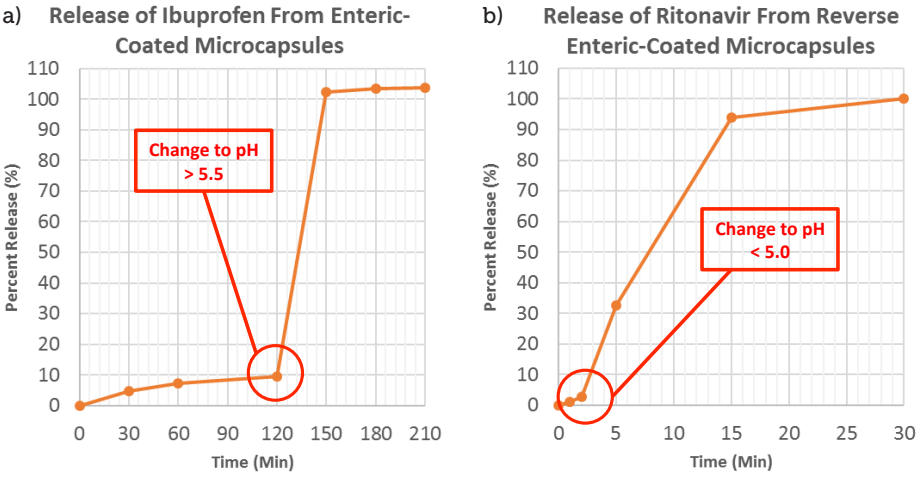

Figure 3: Orbis' Optimμm® technology during dissolution testing showing (a) release of ibuprofen from an enteric-coated microcapsule of diameter 250 μm occurs when the powder is exposed to neutral conditions after an acid soak test of two hours and (b) release of ritonavir from reverse enteric-coated microcapsules of diameter 250 μm occurs when the powder is exposed to low pH conditions similar to the gastric mucosa.

> "Beyond the lens of industrial efficiency, the ability to provide controlled-release kinetics with format-flexible dosage forms is fundamental for serving specific, large populations. When considering just paediatrics and geriatrics, dosage forms that cannot be swallowed or cause difficulty swallowing affect over half of the global population. However the need extends well beyond these patient populations as there are specific therapies and indications that induce dysphagia, even in healthy adults."

With the wide array of enteric and reverse enteric polymers available it stands to reason that new technologies such as the Optimμm® platform will utilise these complex chemistries in unique ways, putting new spins on old dosage forms. This seemingly simple switch from a multi-step process to a single step process provides the industry with the opportunity to increase manufacturing efficiency and lower costs whilst eliminating coating variability for improved product performance.

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forms is fundamental for serving specific, large populations. When considering just paediatrics and geriatrics (under 18 and over 65 years of age), dosage forms that cannot be swallowed or cause difficulty swallowing affect over half of the global population. However the need extends well beyond these patient populations as there are specific therapies and indications that induce dysphagia, even in healthy adults.

The evolution of oral dosage forms to include enterics and reverse enterics showcases the industry's ability to develop solutions for protecting both patient and API. The current multi-step processes needed to manufacture enteric and reverse enteric dosage forms achieve the desired effect but are burdensome and wasteful, often missing the mark in terms of patient palatability or product performance. Orbis' Optimμm® technology provides an elegant solution by condensing all manufacturing steps into one. This solution comes with the added benefit of creating a dispersed, microcapsule dosage form that is ideal for use in multiple format types serving a broad range of patient populations.

ABOUT THE AUTHORS

Nathan Dormer, PhD, is Vice-President of Research & Development at Orbis Biosciences. He has a decade of experience developing a variety of controlled-release solutions using microsphere techniques. He received his BS in Chemical Engineering from The University of Kansas (Lawrence, KS, US) before completing his PhD in Bioengineering with Honors from The University of Kansas with NIH-sponsored training in drug delivery and protein stability. He has authored a number of publications and book chapters relating to microsphere encapsulation and has direct experience formulating dozens of active pharmaceutical ingredients.

Cory Berkland, PhD, is the co-founder and Chief Scientific Officer of Orbis Biosciences. He has been developing micro-encapsulation and drug delivery capabilities for more than a decade. He has a PhD in Chemical and Biomolecular Engineering from the University of Illinois, Urbana-Champaign, where he co-invented and developed the Orbis technology. Dr Berkland is also a Professor of Pharmaceutical Chemistry and Chemical and Petroleum Engineering at the University of Kansas.

ABOUT THE COMPANY

Orbis Biosciences partners with pharmaceutical companies to optimise their oral and injectable product portfolios. Orbis delivers uniformly sized microspheres and microcapsules for precise control over release kinetics in a single manufacturing step. Oral products enabled by Orbis' Optimμm® technology feature taste-masking, extended-release and delayed-release options in patient friendly formats. Injectable products enabled with Orbis' Stratμm™ technology include extended-release and a market pioneering pulse-release option.