

Cover Up

By Elizabeth Shen
at Colorcon

The reasons supporting continuous improvement of film coat formulations for solid dosage forms are clear. Recent research suggests that further study of this area can benefit developers and manufacturers of pharmaceutical tablets, as well as providing patients with a superior product

Film coating of solid oral dosage forms provides a number of advantages – from product protection and packaging efficiency, to improved swallowability, better differentiation and patient compliance. It also functions as a barrier for moisture sensitive, acid-labile or bitter tasting actives. This article will discuss recent advances in each of these areas.

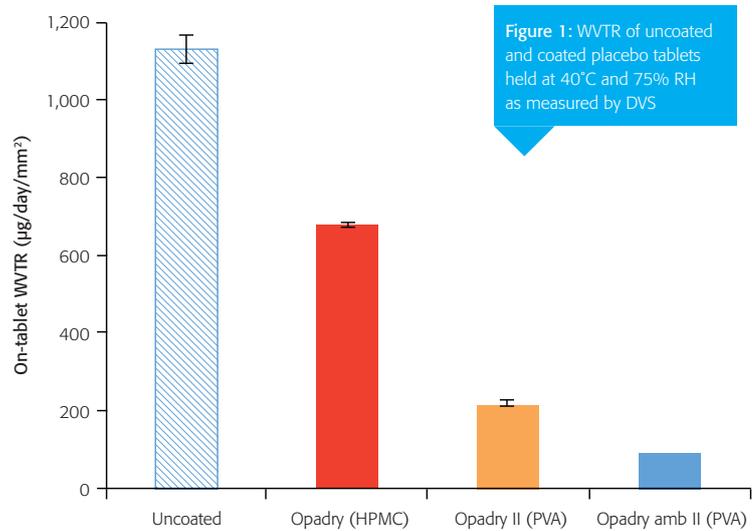
Moisture Protection

There exists a growing class of active pharmaceutical ingredients (APIs) that are sensitive to moisture, with exposure leading to degradation and/or poor efficacy of the drug. It is imperative to develop film coating formulations that can be applied with minimal ingress of water into the tablet, as well as providing protection from humidity in storage (1). Appropriately formulated, immediate-release film coating systems can offer a moisture barrier to improve the stability of these hydro-sensitive compounds.

Dynamic Vapour Sorption

Advances in analytical testing have correlated various methodologies in coating performance.

A recent study evaluated uncoated and coated placebos for film coating moisture barrier properties, using a novel on-tablet dynamic vapour sorption (DVS) model (2).



DVS monitors weight variation due to moisture uptake in an environment of changing humidity and temperature. It has previously been shown that lower uptake values can lead to better moisture barriers (3).

The tablets were initially dried and equilibrated at 40°C and 0% relative humidity (RH). The environment was then adjusted to 40°C and 75% RH, recording moisture uptake by weight change as a function of time, until the tablet reached a steady state. Water vapour transmission rates (WVTR) for tablets – uncoated and coated with 4% weight gain using three different coating systems – are shown in Figure 1. As expected, the uncoated tablet had the fastest rate of water

sorption, while all coated tablets showed significantly lower WVTR values.

Traditional coatings based on hypromellose (HPMC) as the film-forming polymer do impede the uptake of moisture, when compared to an uncoated tablet. However, studying coatings that utilise polyvinyl alcohol (PVA) as the film-forming polymer shows vast improvements in moisture barrier properties over traditional HPMC-based coatings. Opadry® amb II produced the lowest WVTR value, indicating that it offers enhanced moisture barrier properties. In addition, the coating is able to achieve these benefits without the use of polyethylene glycol (PEG), known to react with sensitive drug products.

Keywords

- Dynamic vapour sorption
- Water vapour transmission rates
- Enteric protection
- Taste-masking

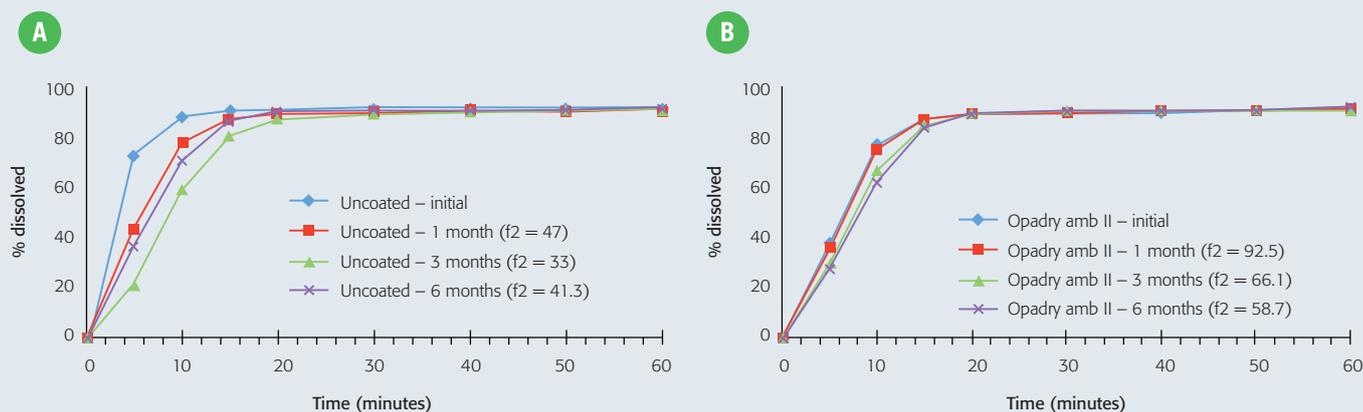


Figure 2: Comparative dissolution profiles of ibuprofen tablets. A: Uncoated; B: Coated with Opadry amb II moisture barrier

Ibuprofen Stability

In another study, ibuprofen was selected as a model drug to further examine moisture barrier performance (4). Coated and uncoated ibuprofen tablets (325mg) were evaluated for dissolution after accelerated stability at 40°C and 75% RH over a six-month period (see Figure 2). Qualitatively, ibuprofen release from the uncoated tablet changed significantly over the duration of the test. In contrast, tablets with PVA-based coatings showed fewer dissolution differences over time at accelerated conditions.

Using the dissolution similarity factor f_2 , the US FDA has set a standard of f_2 value between 50 and 100 to indicate similarity between two dissolution profiles (5). An average difference of 10% at all measured time points results in an f_2 value of 50. The uncoated tablets showed f_2 ranging from 33 to 47, while the tablets coated with a PVA-based film showed release profiles across six months of accelerated stability, with an f_2 range from 58.7 to 92.5.

Enteric Coating

The need for pH-dependent film coatings arises when a drug may be acid-labile, irritating to the stomach, or requiring targeted release in the small intestine for optimal bioavailability. Enteric coatings employ the use of a

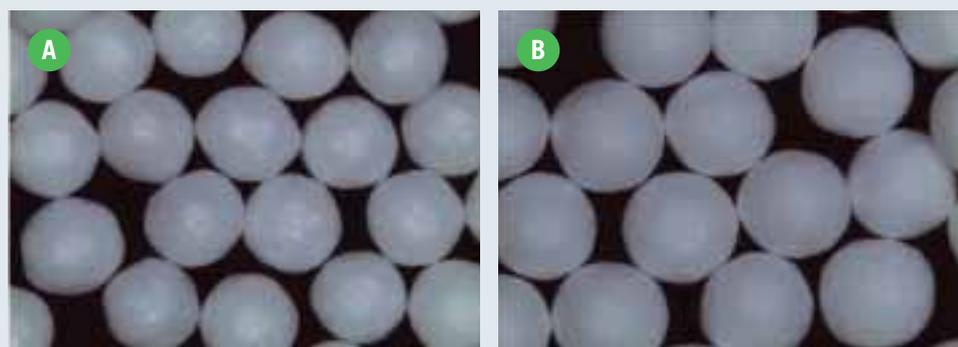
pH-dependent polymer, such as methacrylic acid copolymer – designed to remain intact at the lower pH of the stomach and dissolve immediately in the neutral pH of the small intestine. Proton-pump inhibitors (PPI) require protection at intermediate pH 4.5 due to their acid-labile nature. Acryl-EZE® II is a fully formulated system designed to provide an aqueous acrylic enteric film coating that can remain intact at acidic and intermediate pH (6).

Lansoprazole was used as a model drug to evaluate enteric protection at intermediate pH, as it is acid-labile and also increases stomach pH through its function as a PPI (7). In a Vector VFC-60 fluid bed, lansoprazole was layered onto Suglets® sugar spheres (850-1000 μ m) using Opadry as a binder, with sodium bicarbonate as a buffering agent to improve the stability of the drug. A seal coat was applied to the drug-layered multiparticulates to protect the API from the

inherently acidic pH of the enteric coating. An Acryl-EZE II coating was then applied at up to 40% weight gain to provide enteric protection to the drug-layered beads. Photographs of the drug-layered and enteric-coated sugar spheres are shown in Figure 3.

Enteric performance was evaluated using US Pharmacopeia dissolution apparatus 2, testing the multiparticulates in different media. A solution of 0.1N hydrochloric acid was used to simulate a normal stomach pH 1.2, and an acetate buffer at pH 4.5 was used to simulate a fed state or PPI-treated stomach. After one hour in acidic media, the multiparticulates were transferred into pH 6.8 phosphate buffer for dissolution and drug release testing. An application of 20% weight gain of Acryl-EZE II was sufficient to provide enteric protection to the lansoprazole multiparticulates, while facilitating immediate release upon exposure to a neutral pH (see Figure 4, page 46).

Figure 3: A: Lansoprazole drug-layered sugar spheres; B: Sugar spheres with 40% WG Acryl-EZE II enteric coating



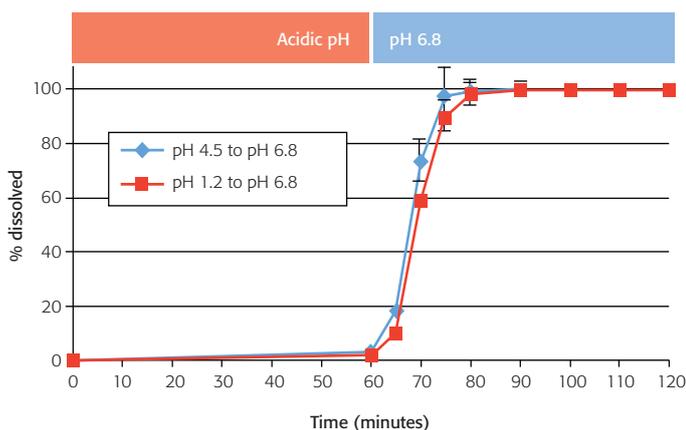


Figure 4: Dissolution of lansoprazole multiparticulates coated with 20% weight gain of Acryl-EZE II at pH 1.2 and 4.5

Taste-Masking

There is a growing need for taste-masking of drug particles due to the ever-changing regulations designed to create dosage forms for specific populations – paediatrics and geriatrics, for example, who may struggle with compliance (8). In some cases, a drug can simply be combined with flavours and sweeteners to become palatable. With more bitter-tasting actives, the drug particle itself must be coated with a barrier to provide taste-masking in the mouth, followed by immediate release in the stomach. One approach to taste-masking is to apply a barrier membrane coating, such as Surelease® aqueous ethylcellulose dispersion, to prevent release in the mouth. The addition of a pore-former, like HPMC, will allow for immediate release in the stomach.

Case Study

Raltegravir is an anti-retroviral drug, developed by Merck Sharp & Dohme (MSD) for the treatment of HIV, and marketed under the trade name ISENTRESS®. The product was first introduced in the EU in December 2007 as a 400mg film-coated tablet for adults.

Subsequently, MSD decided to develop a paediatric formulation of the drug designed to be suitable for children from the age of two years (25mg and 100mg dose) (9).

The active substance has an intense bitter taste, and therefore taste-masking of this material was seen as an essential part of the development programme. Several taste-masking options were evaluated by coating the raltegravir granules prior to processing into the final dosage form. The chosen option was to use a coating comprised of Surelease and Opadry.

In the EU, the paediatric form of ISENTRESS gained a positive reaction from the Committee for Medicinal Products for Human Use in October 2012, for use in children from the age of two years. In the US, there is also an oral suspension version that is licensed for patients

at least four weeks of age and weighing over 3kg.

Substrate Morphology

When developing a strategy for taste-masking, it is important to consider the substrate to be coated – whether a particle, granule or sugar sphere. As with any functional coating, the size, shape and particle size distribution of the substrate will heavily influence the coating efficacy and the release profile of the final product. The optimal starting particle for taste-masking applications is a sphere with a diameter ranging between 150-300µm (10). Finer particles can be difficult to fluidise and are prone to agglomeration in the coating process, while larger particles may lead to an unpleasant and gritty feel in the mouth.

A recent study examined three different grades of paracetamol (Mallinckrodt Pharmaceuticals) for taste-mask coating, with key properties listed in Table 1. Each grade of paracetamol was coated to 10% weight gain using Surelease and Opadry in the ratio of 85:15 in a Glatt GPCG-2 fluid bed. Micrographs of the uncoated and coated materials are also shown.

The finest grade of paracetamol, Compap™ PVP3, demonstrated strong agglomeration during the coating process, resulting in insufficient delay of release for taste-masking (see Figure 5, part A). The two granulated forms of paracetamol, each designed specifically for coating or sachet formulation, showed significant dissolution delay with equivalent coating. This can be explained by the change in coating thickness, due to both differences in surface area, and considerable granulation and agglomeration occurring with the finer particles.

The coated active granules were then compressed into chewable tablets. It was found that the

Table 1: Key properties of paracetamol granules for taste-masking coating

Grade of paracetamol	Manufacturing method	Intended applications	Drug assay (%)	Particle size d ₅₀ (µm)	10% coating weight gain Surelease: Opadry 85:15
* 	Spray drying	Direct compression	95.5-98.5	181.2	
** 	Crystallisation	Encapsulation Coating	99-101	332.2	
*** 	Crystallisation	Sachet Granulation Compression	99-101	473.4	

* Compap PVP3 ** Special granular *** US Pharmacopeia compendial granular

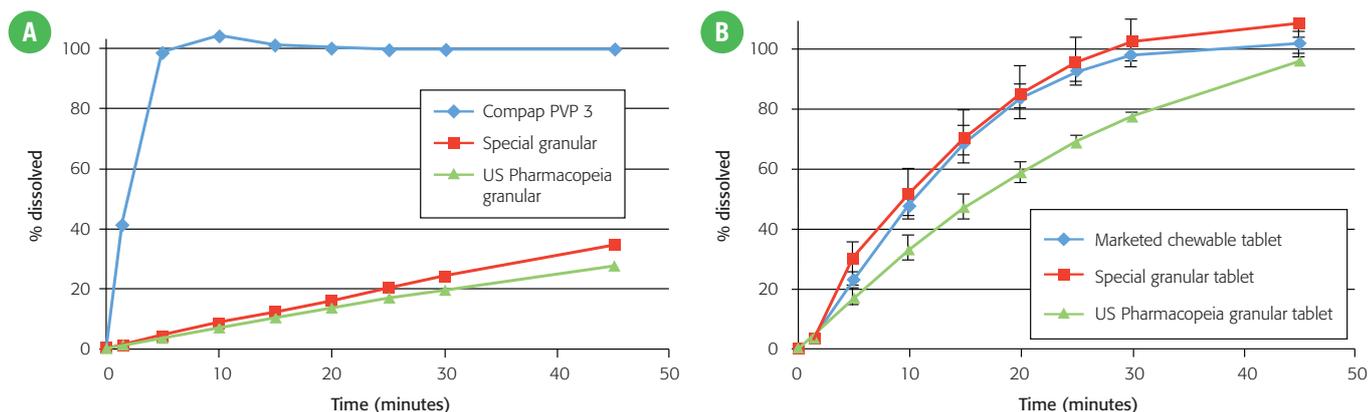


Figure 5: Dissolution profiles of Surelease:Opadry 85:15 coated paracetamol, comparing granules (A) and formulated chewable tablets (B)

paracetamol release rates increased significantly due to partial rupture of the barrier film coating on compression (see Figure 5, part B). Here, commercially marketed product dissolution profiles were matched, and both types of coated granules met the compendial monograph for immediate release of paracetamol (no less than 70% release after 45 minutes).

This work highlights the importance of correct selection of both the substrate and the film coating used in a taste-masking application.

Continuous Improvement

Film coating of solid dosage forms provides benefits for all parties involved. For the formulator, film coating can be used as a tool to target delivery and improve product stability; for the manufacturer, it strengthens the dosage form, enables improved packaging efficiency and prevents cross-contamination; and for the patient, it improves compliance through enhanced swallowability and palatability, allows for better product differentiation, and minimises medication errors through colour and appearance.

All of these advantages build support for the continuous improvement of film coating formulations and processes to create solid dosage forms that are technologically achievable and economically desirable.

References

1. Cunningham C, Farrell T and Quiroga A, Coating moisture sensitive products, Abstracts of posters, Meeting of the Argentinian Association of Industrial Pharmacy and Biochemistry, Buenos Aires, Argentina, September 2005
2. To D, Teckoe J and Rajabi-Siahboomi A, A novel method to evaluate on-tablet moisture barrier performance of Opadry® film coating systems, American Association of Pharmaceutical Scientists Annual Meeting and Exposition, San Diego, CA, 2014
3. Shibaya M *et al*, Effect of soft segment component on moisture-permeable polyurethane films, *Journal of Polymer Science Part B: Polymer Physics* 44: pp573-583, 2006
4. Gimbel J *et al*, Evaluation of a novel, PEG-free, immediate release Opadry® aqueous moisture barrier film coating with high productivity, American Association of Pharmaceutical Scientists Annual Meeting and Exposition, San Diego, CA, 2014
5. Shah V *et al*, Dissolution profile comparison using similarity factor, f_2 , Office of Pharmaceutical Science, Center for Drug Evaluation and Research, FDA, Rockville, MD
6. Young C *et al*, Achieving resistance to a range of acidic pH media using a novel fully formulated Acryl-EZE® enteric coating system, American Association of Pharmaceutical Scientists Annual Meeting and Exposition, San Diego, CA, 2014
7. Young C *et al*, Evaluation of a novel fully formulated Acryl-EZE® enteric coating system vs EUDRAGIT® L30D-55 on lansoprazole multiparticulates at small and large coating scale, American Association of Pharmaceutical Scientists Annual Meeting and Exposition, San Diego, CA, 2014
8. EMA, Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev 2, 2013
9. Diimmler C *et al*, Taste masked formulations of raltegravir, US patent WO2012145446 A1, 25 October 2012
10. Mehta AM, Taste masked pharmaceutical compositions, Patent 5,084,278, 2 June 1989



Dr Elizabeth Shen has over a decade of pharma industry experience, with seven years at Colorcon as a Technical Manager focused on film coatings and development of solid oral dosage forms. Her experience ranges from initial product selection to formulation and troubleshooting of commercial scale processes, supporting many final marketed dosage forms. Elizabeth began her career as a formulator and research scientist at GlaxoSmithKline Consumer Healthcare, and she earned her doctorate from the department of Chemical and Biochemical Engineering at Rutgers University, New Jersey. Email: eshen@colorcon.com