Design, formulation and manufacture of film-coated drug products

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Film coating is a common step in tablet manufacture that can be used to improve product appearance, organoleptic properties, or to facilitate swallowing. Functional film coats can also be used as a part of the product’s stabilisation strategy and to modify or delay drug release.

The film coat, along with the tablet shape and size, defines the appearance of the product. Distinctive colours and shapes can be important aspects of the brand image. Colour also helps patient to distinguish between different medications and is an important aspect of compliance. Patients are more responsive when the colour matches the therapeutic use, e.g., blue is a calming colour and can be useful in sleep medications. Tablet colour is also linked with flavour perceptions – pink is considered to be sweeter than red, whereas, yellow is viewed as salty irrespective of the actual components of the formulation.

Many elderly patients struggle to swallow solid oral dosage forms – a condition called dysphagia. Swallowing can be facilitated by both tablet design (small, caplet shaped) and the presence of a film coat. The US FDA has indicated that the absence of a film coat can either decrease or constrain tablet mobility compared with a coated tablet of the same size and shape.

APIs are typically bitter tasting, and this can be a significant challenge in the development of oral liquid or oral suspension products, particularly for paediatric patients. For oral swallow tablets, this is less of an issue and it can be addressed using a simple aqueous film coat. The coat acts as a physical barrier between the buccal cavity and the API and the dosage form is typically swallowed whole, which minimises the opportunity for solubilised drug to be present in the mouth. However, for dosage forms that are not swallowed whole, e.g., chewable tablets, more bespoke film coating approaches may be required, which can include coating the granules as well as the tablet.
tablet cores. The key design intent is to retard dissolution in the buccal cavity without affecting rapid dissolution in the stomach, ie, to not affect bioavailability.

Ibuprofen can be coated with methacrylic acid copolymer (Eudragit) to form microcapsules, which can be used to form chewable taste-masked granules. Dimenhydrinate can be coated with Eudragit, starch or carboxymethyl cellulose polymers. A chewable paracetamol tablet has also been prepared by compressing coated granules. The API is coated with a mixture of cellulose acetate, cellulose acetate butyrate and hydroxypropyl cellulose, or with cellulose acetate, Eudragit E100 and polyvinyl pyrrolidone.

Functional film coatings
Stabilisation strategy
While pack design, including the use of desiccants, is the principal strategy for stabilising drugs prone to hydrolysis, specialised moisture protective film coatings, eg, Opadry II, Opadry AMB, etc, can provide additional moisture protection. This is particularly appropriate for protection of the bulk product prior to packaging or during transit if packaging is performed at a remote facility.

A recent publication highlighted that moisture protection barriers could stabilise a moisture-sensitive API while also reducing potential incompatibilities with a second API in a fixed-dose combination (FDC) tablet. A drug layered pellet containing a moisture sensitive DPP-IV inhibitor was coated with various different seal coats and moisture barriers. Compression aids were added together with granulated metformin seal coats and moisture barriers. Compression aids DPP-IV inhibitor was coated with various different layered pellet containing a moisture sensitive API while also reducing moisture protection barriers could stabilise packaging is performed at a remote facility. In these cases, the design intent is to delay release until the colon and this is achieved by polymers that release at above pH 7 using Eudragit S, Eudragit FS and other suitable polymers.

Some products use both approaches, with the first layer dissolving in the small intestine (> pH 5.5) releasing part of the product, and the second coat dissolving in the colon (> pH 7). This can be achieved using either layer coating or the preparation of two different coated granules. An example of the latter approach was described by Howden. The product was comprised of two PPI granules: the first component released one to two hours after dosing and provided day-time treatment for gastroesophageal reflux disease (GORD); the second component released about five to six hours after dosing and addressed breakthrough GORD often seen in the late evening or overnight.

Based on the variable gastrointestinal pH observed within the general population (and especially with colonic-pH), the effectiveness of colon-targeting using pH alone (pH > 7) has been widely questioned. Several alternative strategies have been proposed. Resistant starch or high-amylose maize starch can be blended with Eudragit S polymer to facilitate reproducible colonic-release. This approach relies both on colonic-pH and selective microbial degradation of the starch in the colon. This approach demonstrated consistent release at the ileocecal junction (ICJ) or within the colon, irrespective of dietary conditions. A layer-coating approach utilising an outer layer of Eudragit S and an inner alkaline buffered layer was also developed. This ensured that the inner alkaline layer (pH > 7) promoted the dissolution of the polymer permitting targeted release at the ICJ. This concept was demonstrated using scintigraphy in human volunteer studies. Disintegrants can also be added to the Eudragit S layer to facilitate targeted release. Studies in fasted human volunteers showed

Delayed release
Classically, enteric coating with pH-sensitive polymeric coats has been used to delay the release of certain medicinal products. This is either to protect the product against the acidic environment in the stomach, eg, proton pump inhibitors, or to protect the stomach against gastric bleeding from the routine use of non-steroidal anti-inflammatory drugs like aspirin. As such, acid-resistant polymers, eg, Eudragit L, Kollicoat D and Kollicoat DP, have been commonly used to prevent release at pH 1.2, with enhanced solubility at pH over 5.5, thereby by-passing the stomach and releasing the drug in the small intestine. Some delayed-release products, eg, 5-aminosalicylic acid (5-ASA), are systemically toxic and are used for topical treatment in the colon for irritable bowel disease. In these cases, the design intent is to delay release until the colon and this is achieved by polymers that release at above pH 7 using Eudragit S, Eudragit FS and other suitable polymers.

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Aqueous film coating processes can still present significant challenges to moisture-labile APIs.
reproducible release in the caecum and colon using this approach.23,24

Modified release
Modified-release (MR) dosage forms can be simplistically divided into two main types: either matrix tablets or multiparticulates, where the release-controlling polymer is added as a pH-sensitive film coat.25 Drug dose in a multiparticulate delivery system is divided across the whole system; therefore failure of a few units will be significantly less severe than the failure of a single-unit matrix tablet system, ie, dose dumping.

Multiparticulates typically comprise inert spherical particles, ie, nonpareil seeds layer-coated with drug and various functional and non-functional film seal coats. This approach can be used to achieve MR release profiles, delayed and/or targeted release, and/or pulsatile release. A recent review summarised the various different multiparticulate approaches, eg, swelling/rupturing, dissolution and/or erosion, and modification of the intrinsic permeability of the film coat.26 Many different polymers have been evaluated as coatings for multiparticulate systems; some of these include Eudragit RS/RL, starch acetate,27 ethyl cellulose28 and Eudragit S.29 In addition, aqueous or organic film coating can influence the performance of the polymer and the release profile of the resultant product.21

Pulsatile delivery could be achieved by layering of nonpareil cores with an active layer, a swelling layer comprising a binder and superdisintegrant, eg, Ac-Di-Sol, sodium starch glycolate, and an insoluble, water-permeable polymeric coat, eg, ethyl cellulose.30 Similarly, the permeability of ethyl cellulose coats (and thereby the release profiles) could be easily modified in a pH-independent fashion by adding varying levels of polyvinyl alcohol/polyethylene glycol.29

Several quality by design (QbD) approaches to the optimisation of different types of polymeric film coats have been published.27,28 The former statistically assessed three critical processing parameters (CPP), ie, plasticiser concentration, polymer ratios (Eudragit RS/RL) and coat weight. The optimised formulation delivered a release profile in line with predictions.27 Similarly, three comparable CPPs, ie, curing temperature, plasticiser concentration and coat weight, were assessed in the latter case. The drug release profiles were again aligned with model predictions.28

Dose dumping
Many modified-release (and some delayed-release) products contain higher levels of active than the corresponding instant-release product. Therefore, dose dumping is a major risk for these dosage forms. That is, the potential for the drug to be released instantaneously, rather than in a controlled fashion over several hours. The situation is most concerning for drugs with narrow therapeutic windows, eg, theophylline. Dose dumping has also been reported to occur in the presence of alcohol. FDA requested the withdrawal of once-daily hydromorphone as a result of alcohol-induced dose dumping.32 Some polymeric excipients, eg, Eudragit, are more soluble in the presence of alcohol and this affects their ability to retard release of the drug and leads to dose dumping. For other excipients, eg, hydroxypropyl methylcellulose (HPMC), alcohol retards swelling of the tablet matrix and inhibits the release-controlling mechanisms.34,35

There are now requirements to perform in-vitro dissolution testing in hydro-alcoholic media for both modified- and delayed-release products.36 Since Eudragit-based polymers are heavily used in functional coats there is obviously a risk associated with these types of product. Three mesalamine (5-ASA) delayed-release/extended-release products were tested for dose dumping in the presence of hydroalcoholic media. The two delayed-release products were enteric coated, whereas the extended-release product used an ethyl cellulose matrix tablet approach. Alcohol compromised the integrity of the enteric coat during the acid stage of the test and the drug was released much earlier than intended (distal end of small intestine/colon).37,38 Similarly, alcohol affected the release rate from the ethyl cellulose extended-release product.39

A significant number of patients are now prescribed proton pump inhibitors that typically increase gastric pH to values greater than 4.0 (cf, pH 1.2 in the ‘normal’ population).39 This can potentially have a significant effect on enteric coats, which are designed to be insoluble at pH 1.2 and to solubilise at pH > 5.5.40

Conclusions
Film coating is commonly used in tablet development to address certain universal challenges. Dysphagia, poor palatability and brand image can all be addressed using non-functional film coats. Stability can often be improved by the judicious selection of a film coat with decreased moisture permeability. pH-sensitive film coats are typically used to delay or modify drug release to facilitate improved patient outcomes. However, the high pH variability seen in typical patient populations, often exacerbated by co-medications such as PPIs that increase gastric pH to over 4.0, can compromise the clinical utility and safety of these pH-sensitive film coats. This can be addressed by modifying the permeability of these film coats with additives such as superdisintegrants, basifiers, or microbial sensitive excipients.