THIN FILM EVOLVES TO LEVERAGE MUCOSAL DRUG DELIVERY BENEFITS

The use of thin film drug delivery systems is growing in importance as the benefits, such as improved drug bioavailability, reduced adverse events and avoidance of the first pass metabolism, are increasingly being recognised. Megan Greth and Scott Barnhart from ARx look in more detail at what this method can offer.

Although thin film drug delivery products have been on the market for nearly a decade, there are still many unmet patient and market needs that can be solved with this type of delivery system.

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The first drug delivery products developed were over-the-counter medicines, in which the drug was swallowed orally and absorbed in the gastro-intestinal (GI) tract. While offering many convenient benefits to the patient, such as discrete packaging, ease of transporting and ease in dosing without water, the dosage form has since evolved to capitalise on the benefits of mucosal drug delivery (Figure 1).

The specific benefits of mucosal thin films include the potential for improved onset, enhanced active pharmaceutical ingredient (API) bioavailability, reduction in adverse events and avoidance of the first-pass metabolism. With more products emerging in development pipelines and regulatory approvals, the potential for mucosal thin film delivery is finally gaining recognition.

MAXIMISING THE BENEFITS OF THIN FILM DRUG DELIVERY

In order to develop an optimised mucosal thin film product, it is important to:

- Understand the mucosa and the benefits of the thin film dosage form
- Engage with experienced formulators who can properly customise the thin film properties
- Select the appropriate API.

Improved Bioavailability

Due to the permeability of mucus membranes, it is well known that improved bioavailability of an API can be achieved through bypassing the first-pass hepatic clearance and avoiding the degradation or elimination of drug in the GI tract, which is common for traditional dosage forms, such as oral tablets and capsules.

Additionally, the buccal mucosal and the sublingual area have the appropriate features to be among the best suited for local and systemic drug delivery.[1] However, the sublingual mucosal membrane is nearly 400 µm thinner than the buccal mucosal membrane, at approximately 190 µm.

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By leveraging the permeability of the mucosal membranes, one can see the distinct advantages mucosal thin films have over traditional oral thin films. Due to the direct contact with the mucosal tissue and high vascular perfusion, mucosal thin films offer rapid onset and the potential to improve upon T_{max} over other currently available immediate-release oral dosage forms.

Reduced Adverse Events

By selecting the mucosal route of administration over oral ingestion and subsequent GI absorption, formulators may be able to load less API in the film, resulting in additional cost savings and reduced adverse events. Through product design, formulators can also minimise the amount of the drug to be swallowed, which has the potential to decrease the adverse event profile further depending on the drug and specific metabolites.

This is an important consideration for drug developers as the Centers for Disease Control and Prevention (CDC) classifies Adverse Drug Events (ADEs) as a serious public health problem and estimates that 700,000 emergency department visits and 120,000 hospitalisations are due to ADEs annually.[2] Subsequently an additional US$3.5 billion (£2.6 billion) is spent on extra medical costs of ADEs.[3] In addition to these startling numbers, the CDC also predicts that the number of adverse drug events is likely to rise for several reasons such as an increase in new treatment therapies and the ageing population.

Adverse drug events translate to a large concern for drug development companies, as they affect the patient's quality of life, undermine the value of a drug in the face of heavy scrutiny by payers and can easily be disseminated on the internet or via patient advocacy groups.

In a 2013 *Clinical Informatics News* article, the author cites strategies and considerations for proper drug reimbursement which include:

- Phase II and Phase III clinical trial design
- Payer engagement
- Understanding the current reimbursement environment
- Recognising competitive strategies
- Creating portals for patient access.

In addition, the value must continue to be demonstrated during commercialisation of the drug product. "Payers gradually will become more discriminatory in coverage. Increasingly they want to see real, not modeled, data on saved hospitalisation costs with outpatient use."[4] By using a mucosal thin film drug delivery system, companies can demonstrate the value of their drug to payers through a reduced ADE profile in comparison to other available options.

Figure 1: Mucosal thin film delivery is a convenient and efficacious dosage form.

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Tailored Properties and Characteristics

The thin film dosage form can be easily customised and tailored. Through careful selection and marrying of excipients, formulators can achieve a range of physical properties within a film. Examples of such excipients are cellulose derivatives, gums, polysaccharides and hydrocolloids. These excipients are generally regarded as safe (GRAS) and listed in filed products with the FDA for various thin film products and other approved dosage forms.

When selected appropriately with an understanding of excipient functionality, it is possible to tailor many physical characteristics such as drug concentration, dissolution rate and disintegration time. Dissolution and disintegration time easily range from mere seconds to an hour of residence on the mucosal tissue.

In combination with the API, the physical properties influence a tailored target pharmacokinetic profile. Each of the physical characteristics can also be tailored in the different layers of a multi-layer system, where each layer serves a specific function such as API compatibility or penetration enhancement. FDA-approved products already utilise a bilayer mucosal system, in which a backing layer can

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be designed to erode at a slower rate and protect the muco-adhesive layer, while ensuring drug penetration in a uni-directional manner. In addition, a variety of FDA colours and GRAS flavours can also be utilised for brand recognition and continued product lifecycle management for these special systems.

CONCLUSION

By forging partnerships that leverage the API, clinical, patient and regulatory knowledge of the NDA holder with the thin film formulation and process expertise of the developer, mucosal thin films can help to change the landscape of drug delivery and define product value, while providing solutions to a large unmet medical needs.

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