# ORAL THIN FILMS: NOVEL MANUFACTURING TECHNOLOGY & ITS CHALLENGES

Presented from both the technology and formulation perspectives, here, Nidhi Prakash Sapkal, PhD, Principal Research Co-ordinator, and Anwar Siraj Daud, PhD, Managing Director, both of Zim Laboratories, discuss the challenges of industrialising oral thin films, a promising but difficult dosage form.

## INTRODUCTION

In the last decade, oral thin films (OTFs) have been gaining widespread acceptance as a drug delivery solution amongst pharma manufacturing companies. These films have significant visual and functional differences from the other solid oral dosage forms, such as tablets and capsules, and thus provide strong product differentiation. The fact that these films disintegrate and dissolve in the mouth makes them particularly desirable for certain patient groups, such as paediatric, geriatric, dysphagic and bed-ridden patients. Table 1 describes some such patient populations and their specific needs.

Thin films are an innovative technology platform that is amenable to a wide product range. Many molecules, across various therapeutic segments, can be developed in this form. It provides immense benefits for the intended patients, clinicians, carers and other stake holders, such as those in the supply chain. Table 2 lists the benefits of OTF technology to various stakeholders.

> "Pharmaceutical thin films can be manufactured by using either solvent casting or melt extrusion. At present, commercially available films predominantly use solvent casting."

| Patient Type | Examples of Specific Needs and Problems |
|---|---|
| Paediatric | • Uncooperative patients<br>• Prescribed liquids as they can't swallow pills<br>• Liquid formulations are associated with administration of imprecise doses<br>• Liquids have handling, storage and transport problems |
| Geriatric | • With increasing age, swallowing is more difficult<br>• Because of many chronic problems, pill burden is high<br>• Dependent upon caregiver |
| Dysphagic | • Inherent difficulty in swallowing |
| Suffering from neurological disorder | • Uncooperative patients<br>• Voluntary swallowing absent<br>• Tendency to spit out the medicines |
| Bed ridden | • Difficult to sit in upright position to consume water<br>• Dependent upon caregiver |
| Nauseous because of other primary problems like emesis, migraine | • Consumption of water, or anything, potentiates nausea and triggers emesis<br>• Medication with rapid onset of action is highly desirable |
| Suffering from urology related problems, or anorexic | • Consumption of water leads to worsening of symptoms like increased diuresis or reduced appetite. |

Table 1: Problems and requirements of different patient groups which drug delivery can address.

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| For Patients | For Clinicians | For Manufacturer | For Supply Chain |
|---|---|---|---|
| • Administration convenience, treatment adherence and affordable cost<br>• Value addition in terms of dosage frequency, ease of handling & storage<br>• Increased safety due to lowest excipient load and child resistant packages<br>• No specialised instructions for handling the dosage form | • Provides potentially faster onset of action<br>• Provides solutions to unmet medical needs<br>• No change in the existing dosage and frequency<br>• Makes an alternative solid dosage form available, with more convenient administration to patient populations with specific needs | • Robust process, easy to leverage over many therapeutic categories<br>• Strong IP protection, results in strong technology barrier<br>• Meets all regulatory requirements of target geography | • Flexibility, and ease of storage and transportation |

Table 2: Benefits of OTF Technology to the various stakeholders.

## TECHNOLOGICAL CHALLENGES

Pharmaceutical thin films can be manufactured by using either solvent casting or melt extrusion. At present, commercially available films predominantly use solvent casting. With this method, a solution of hydrophilic polymers and other functional excipients is deposited on a substrate in predetermined thickness. This wet film is then dried; in the literature, there are reports of bottom drying, top drying, alternate-surface drying or a combination of all such processes. Several variations in this basic method have been proposed in the literature in order to get stable films with desirable characteristics, but not all of them have the potential for industrialisation. Some novel methods of manufacturing of OTFs with novel attributes are discussed here along with challenges involved in their industrialisation.

### Fuisz and Fuisz

Fuisz and Fuisz[1] describe a single-layer film with the benefits of a double-layer film. The product obtained using their method exhibits different dissolution behaviours from each side of the film. The product can be used for buccal or sublingual administration where drug release from one side of the film is desirable. The method has advantages over methods of manufacturing double-layer film, where two films are manufactured separately and then placed together.

Here, the difference in dissolution is achieved by adding a hydrophobic material of different density than the other film-forming materials. Such a dispersion, upon deposition to a support surface, shows sedimentation of the hydrophobic material in the thickness direction of film. The extent of sedimentation will depend upon the time the wet film is kept undisturbed before drying.

In the course of industrialising this invention, a major challenge will be critical control of process parameters to obtain films of consistent quality. Since the hydrophobic material is meant to sediment upon layering of the film, it will also tend to sediment during the dispersion stage before layering, therefore continuous stirring is recommended for such dispersions during manufacturing. However, the stirring process will have an impact on the particle size and hydrophobicity of functional materials. This will further affect uniformity of the final films and their intended dissolution profiles. This challenge will be particularly significant for large commercial batches, as process durations will be long.

### Vrbata

Vrbata[2,3] described an electrospinning method for producing nanofibre-based fast-dissolving films. Such films are very interesting as they offer advantages of both nanotechnology and thin films in one delivery system. They have demonstrated higher solubility and improved bioavailability. These films therefore have significant advantages over currently available OTFs.

Currently reported techniques for manufacturing of nanotechnology based films involve making nanoparticles separately and then putting them in a film-forming dispersion. The method described by Dolezal is a single-step process which, though highly useful, poses several challenges to industrialisation when looking to produce product of consistent quality. Uniformity in nanofibre dimensions at large scale would require an unfluctuating voltage, and consistent spray rate and substrate speed, along with many other factors.

Moreover, the dose uniformity in the film is directly controlled by spray pattern. Maintaining such strict control of spray pattern is a challenge. The electrospinning process involves deposition of nanofibres on a conductive surface. Many pharma-grade substrates are not conductive in nature and thus will interfere with the electrospinning process. All these challenges need to be addressed before industrialisation of this delivery system.

### Monitoring OTF Manufacture

OTF manufacturing is, in general, an in-line process with a short manufacturing cycle, therefore critical monitoring of all the process parameters is very important. There are many differences to the in-process monitoring controls and off-process testing compared with conventional dosage forms. For instance, in the case of tablets, uniformity in weight is important, whereas for OTFs uniformity in thickness is an important parameter. The controls are devised to monitor change in film thickness during various stages of casting.

In case of tablets, moisture content needs to be determined only once after granulation, but in OTFs, strict monitoring of moisture content is required during all stages of processing as this determines shelf life of the product in a significant way. Higher than the desired moisture content may lead to chemical instability of the active ingredients, while lower than the desired moisture content may make a film brittle. In summary, the technological challenges are:

- Availability of manufacturing equipment compatible with the technology
- Obtaining robust manufacturing process: high-speed manufacturing of consistently uniform product for long batch runs
- Criticality of online process monitoring due to short manufacturing cycles
- Modification of analytical testing equipment and methods
- High-dose drug loading can interfere in the film formation
- Size and weight can't be increased beyond a limit.

### Melt Extrusion

Melt extrusion is not useful for manufacturing of thin films as the films obtained are not as fast dissolving as those obtained using solvent casting. In this process, the polymers suitable for the melt extrusion process are melted in the presence of other ingredients and subsequently extruded in the shape of films. Because of this melt-solidification process, polymers exhibit varied film forming properties. Additionally, thermo-labile APIs can't be processed using this technique. This is the reason that melt extrusion is not popular for commercial manufacturing of OTFs.

## FORMULATION CHALLENGES

There are formulation challenges unique to OTFs due to increased moisture content, high drying temperatures and overall weight constraints. The properties of the film critically depend upon the properties of the drug molecules, such as hydrophobicity, bulk density, solubility and particle size.

Many APIs have been found to interact with film-forming materials that modify their casting behaviour and processability. It has been seen that for the same film-forming composition, different APIs at the same dosage level and with similar processing conditions result in films with different properties, including solubility, tensile strength, percent elongation, disintegration time and disintegration behaviour in the mouth. This is because these APIs interact differently with the same film-forming composition, therefore altering the OTF properties.

> "Since the attraction to this dosage form derives from its low weight and uniform thinness, these cannot be compromised in any way during development."

On the other hand, drug molecules have also been found to show different physicochemical properties with different film-forming polymers. APIs like ketorolac tromethamine and levocetirizine have been found to exhibit different polymorphic forms when processed with different film-forming polymers. Needless to say, such behaviour affects product stability drastically. Studies have revealed that, for the same polymeric composition, different drying temperatures of the films not only affect folding endurance, tensile strength and stability of the APIs but also their release behaviour. This happens because of a change in the nature of interactions between the drug and polymer at different temperature.

Another major challenge lies in the development of taste-masked films for bitter APIs. There are several taste-masking techniques, however these taste-masked complexes or intermediates further interfere with the film-forming properties of polymers and pose challenges to developing films with the desired attributes. Challenges also lie in selecting the number of enabling excipients that can be used as solubility enhancers, taste modifiers and stabilisers. It is worth remembering throughout that, since the attraction to this dosage form derives from its low weight and uniform thinness, these cannot be compromised in any way during development.

## CONCLUSION

In general, the manufacture of fast-dissolving OTFs is a very challenging process. As mentioned in the beginning of this article, there are several techniques disclosed in the literature that result in OTFs with novel and advanced features. However, converting those techniques into usable technologies is a real challenge. This is the reason that there are presently very few products in the market that are manufactured using such techniques.

## ABOUT THE COMPANY

Zim Laboratories is an innovative drug delivery solution provider focusing on improving patient convenience and adherence. It offers a range of technology-based drug delivery solutions and non-infringing proprietary manufacturing processes for production and supply of innovative and differentiated generic pharmaceutical products. Zim manufactures a comprehensive range of value-added solid dosage products in semi-finished and finished categories. These include granules, pellets (sustained, modified and extended release), taste-masked powders, suspensions, tablets, capsules and its recently developed oral thin films.

## REFERENCES


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## ABOUT THE AUTHORS


**Dr Nidhi Sapkal** is Professor at Gurunanak College of Pharmacy and Principal Research Co-ordinator at Zim Laboratories. She started her career 21 years ago as an academic. At Zim, she is actively contributing to R&D involving novel products and process technologies. She leads various activities related to new product development involving thin film technology including project management, intellectual property, clinical and regulatory. Dr Sapkal has about 25 research papers and 20 patent applications to her credit, and has delivered many lectures at international conferences.

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