Rapidly dissolving oral thin films (OTFs; see Figure 1) are widely accepted by patients and caregivers for their ease-of-delivery, portability and accurate dosing. Since the first commercial launch of OTFs for systemic drug delivery in 2004, the platform has evolved as more pharmaceutical researchers evaluate ways to apply the benefits of this technology across more markets and therapeutic classes for localised and systemic drug delivery.

As a result of these efforts, new applications are emerging. Advances in chemistries and the manufacturing processes used in the formulation and scale-up of this technology play a significant role in advancing the potential of OTFs beyond immediate-release oral applications.

**OTF FORMULATION**

The chemistry and art behind formulating OTFs draws on polymer expertise derived from traditional solid, buccal and transdermal dosage forms. By understanding these formats and leveraging their similarities, formulators can effectively deliver unique and compliant products within a shortened product development timeframe.

The formulation flexibility of the OTF platform enables formulators to evaluate a broad range of excipients and active pharmaceutical ingredient (API) forms when embarking on new product development initiatives. This formulation flexibility may also increase a programme’s chance for success by presenting chemists with a wider range of available material sets to produce both an acceptable and stable product.

When selecting an OTF to replace an existing product, the film’s dissolution rate, material selection and absorption rate are all considered so that an equivalent or an improved product profile may be produced over existing liquids, capsules and tablets. The robustness of thin-film dosage forms has been demonstrated through 24-month ICH stability studies.

Ongoing research is extending the dissolvable film technology to more complicated systems for modified or controlled release. This also includes applications for topical delivery. In some cases, there is convergence with transdermal technology that enables films to have more tangible adhesive properties such as increased dwell time in the mouth or other alternative delivery sites. This work relies on a strong understanding of the suitability, compatibility, and availability of material sets.

**EXCIPIENTS**

Robust OTFs are developed using current commercially available generally regarded as safe (GRAS) excipients. Most major excipient suppliers of solid oral dosage forms materials now offer excipients that are appropriate for use in OTFs and potentially enhance disintegration properties.

The majority of film formulations are first compounded as a liquid prior to being cast into films. A host of water, solvents, and combinations of both exist as process aides. Based on the solubility and compatibility of the API, a formulator can choose to develop a 100% water-based system; or in the event that the API degrades in water, other pharmaceutically-acceptable organic solvents can be selected. Solvent selection can also be used to enhance manufacturing efficiency based on the relative
energy required to remove the volatile liquid during the film casting process.

**RELEASE LINERS**

Significant research and expertise derived from the transdermal arena has resulted in a wide range of release liner technologies that may be used as processing aids in the manufacture of OTFs. These materials are comprised of a plastic film or paper substrate coated with silicone or non-silicone chemistries for a clean release of the film when appropriate in the conversion process. By coating a compounded liquid formulation to a continuous web of release liner material, film manufacturers are able to maintain the integrity of the OTF film product throughout the manufacturing process because this component provides added strength, support and environmental protection to wound rolls of OTF film prior to finishing. Release liners can be incorporated strictly as a processing aide that is removed in the film finishing stage, or as seen in new product launches, this component can remain affixed to the OTF to aid in dispensing and administering the drug product.

**ACTIVE INGREDIENTS**

OTFs can integrate most available forms of APIs, including micronised, granulated, salt, and free-base forms. Both soluble and insoluble drugs have been successfully compounded into solutions, emulsions, or dispersions that have subsequently resulted in the launches of the OTF products currently available in the market today. Larger particle size compounds do present some constraints in regards to the final OTF’s thickness, but in general, most APIs and nutritional compound particle size distributions fall within typical OTF production requirements.

A number of taste-masking options exist and have been used in the development of OTFs. This includes sophisticated masking technology specifically designed for highly bitter materials with an affinity for the oral cavity. Key considerations in selecting any taste-masking approach beyond palatability include cost, impact to API particle size or mass and solvent compatibility.

Researchers have some latitude in both how much API can be incorporated and how other product attributes can be tailored for each thin film drug product. API concentrations are typically limited to 50% of the final unit mass. However, the size of the final unit strip is adjustable to deliver the proper dose. Thicker OTFs can be produced to yield higher strengths. In this case, it is up to the formulator to determine at what point the thickness of the product detracts from the desired disintegration profile. Furthermore, a formulator can elect to produce multiple formulas to obtain multiple strengths for a specific API or produce a single formula that is cut into multiple strengths based on the size of the unit area. For

![Figure 1: Rolls of dissolvable films (left) and film being wound on a roll (right).](image)

![Figure 2: Formulators can choose to produce a single OTF formula that is cut into multiple strengths based on the size of the unit area.](image)
example, 10 mg strength of a given formula could become a 5 mg strength dose by halving the unit size with no additional formulary work required (see Figure 2).

Looking forward, the use of micronised and nano particle APIs in OTFs opens the door for potentially more effective drug delivery methods. With the increased surface area of the API and the larger direct-contact surface area of the film, there is the possibility to improve bioavailability and to increase uptake from the mucosal surface. By modifying the residence time of the OTF on the mucosal tissue in conjunction with the micronised or nano-API, early stage work suggests that this type of system has the potential to effectively deliver drugs in a shorter timeframe.

**OTF MANUFACTURE**

Based on precision adhesive coating technologies used for decades in the transdermal industry, the manufacturing techniques for OTFs are well-understood and lend themselves to holding exceptionally tight tolerances throughout the process. The precision-coating techniques derived from transdermal production are now used for producing OTF base chemistries into final individual doses with unit tolerances as tight as ± 2.5% around the potency target. Specialised coat-weight monitoring systems and liquid deposition techniques enable any OTF product to hold and maintain consistent cross and downstream uniformity during manufacture. This continuous process monitoring also lends itself to process analytical technology (PAT) initiatives and identifying any processing variability in real time (Figure 3).

Coating technology from other markets continues to advance OTF production and cost-effectiveness. Multi-functional mixers drawn from the food industry enable multiple products to be manufactured out of the same process footprint. New approaches in coating techniques are leading to more sophisticated OTF constructions. An example of this can be seen in the adhesive coating techniques utilised in the electronics market for enabling multi-lane simultaneous coating. By applying this technique to OTF manufacturing, the potential exists to coat incompatible materials, or synergistic chemistries, side-by-side without triggering any pre-dose reaction.

Packaging has commonly been a single-unit dosage format that accommodates one or two strips per pouch and enables portability of the product. It also allows for multiple-count options to accommodate dispensing needs and regional requirements. However, a number of new, stable formats are emerging that maintain dose integrity while also offering a more cost-effective dispensing option that complies with stability and regulatory requirements.

The manufacturing flexibility of OTFs reduces capital requirements and capacity consumption. It also enables formulators to consider new options for delivery. Because these manufacturing approaches are also well understood and controlled, robust, efficient development can occur from bench to commercial scale.

**THE FUTURE OF OTFS**

The application of OTFs now extends beyond traditional immediate release oral dosage forms. Development of topical films, probiotic strips, and controlled-release OTF products are new forms made possible through this delivery format’s flexibility, proven robustness and stability.

The future of OTF formulation and processing is a direct reflection of evolving healthcare needs. Demographically, most established markets have aging populations that benefit from simple, easy-to-dispense and dose products. As emerging markets require flexibility in the number of units dispensed at any given time and providers continue to look for options that can increase compliance, minimise dosage levels and frequency, and reduce costs, OTFs have increasingly become the solution to satisfy all of these needs. In addition development teams are able to capitalise on the flexibility of OTFs by adapting the technology for their program.

**ABOUT ARX, LLC**

ARX, LLC, a wholly owned subsidiary of Adhesives Research, Inc (AR), was created in 2005 to address the growing global need for innovative delivery of active drug-containing systems. This was a natural extension of AR’s 20+ years of experience manufacturing pressure-sensitive adhesives and components for transdermal and other pharmaceutical applications.

ARX is dedicated to developing and manufacturing innovative pharmaceutical products, including adhesive laminates and dissolvable films, for customised drug delivery platform technologies. As part of this commitment, in 2007, ARX opened a new, state-of-the-art 25,000 square-foot (2,323 m²) pharmaceutical manufacturing facility designed to manufacture dissolvable film, transdermal, and buccal drug delivery systems for over-the-counter, prescription and biopharmaceutical products. The globally-compliant facility triples ARX’s manufacturing capacity and laboratory space to support the rapid growth in the industry.

**REFERENCES**