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TREATING THE NEXT GENERATION: THE UNTAPPED POTENTIAL OF ORALLY DISPERSIBLE FILMS

In this article, Keat Theng Chow, PhD, Head of Applied Sciences Pharma, Greater Asia, at Roquette, explores the latest scientific thinking on orally dispersible film formulation, and how these advancements could open a new chapter in paediatric patient compliance.

"Children are not just small adults."[1] First coined by the EU's 2007 Paediatric Regulation, this phrase increasingly reflects the pharmaceutical industry's approach to children's medicine. Gone are the days when young patients were forced to make do with smaller doses of drugs authorised for adult use.

Now, regulators and brands alike are allocating significant research and development budgets to find the ideal formulations and dosage forms for paediatric medications. Despite this shift, however, there is a particular delivery method that is yet to receive the attention it deserves as a solution to the challenge of making medications, safer, easier and generally more fun for kids to take.

Orally dispersible films (ODFs) have long been recognised as valuable assets in the ongoing medication compliance conversation. Portable, palatable, easy to administer and offering functional benefits such as reduced first-pass metabolism, faster onset of action and improved bioavailability, these convenient dosage forms are ideally suited to the needs of paediatric patients. But, despite these obvious advantages, recent research suggests just 1% of children favour ODFs compared with more traditional delivery methods such as tablets and capsules.[2]

This disconnect could be related to issues such as awareness, accessibility, efficacy – or a combination of all three. Besides, manufacturers of ODFs face a range of challenges – from ensuring drug solubility and stability to improving production efficiencies to get drugs to market faster. Fortunately, new technologies, excipients and production strategies are emerging to open up the true potential of ODFs and give children the fun and functional treatment options they actually need.

CHANGING PERCEPTIONS OF CHILDREN'S MEDICATIONS

The debate over whether the benefits of specialised paediatric treatments outweigh the ethical concerns of involving children in clinical trials has raged for decades.[3] Until the 1980s, there were few standardised protocols for administering drugs to children, meaning healthcare providers were often forced to adapt medicines only authorised for adults by amending dosages or delivery forms according to their own experience.[3] This "off-label" approach was standard practice for paediatricians across Europe and North America, despite the increased risks of delivering ineffective or even harmful treatments.

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Figure 1: Healthcare professionals increasingly agree that the unique treatment needs of children require the development of specialised medications.

"The consensus today is that the unique physiology and healthcare needs of children require and deserve specialised treatments."

Around the mid-2000s, we began to see this picture shift towards the modern conception of paediatric pharmaceuticals – namely, that there was a clear need for drugs tested and approved for use by children.[3] The EU's 2006 investigation into the availability and efficacy of medicines for patients aged 0–17 years reflected this change in attitude, concluding that there was a serious lack of consistency and knowledge surrounding children's pharmaceutical provision. Across the Atlantic, US lawmakers recognised a similar issue, passing the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) in an attempt to improve healthcare outcomes for young patients.[4]

The consensus today is that the unique physiology and healthcare needs of children require and deserve specialised treatments (Figure 1). Incredible progress has been made in this area over the last 15 years – with more than 260 new medicines for use by children authorised in Europe between 2007 and 2016,[3] and a further 700 products adding specific paediatric use information to their labels across Europe and the US.[5] But much work remains in several key areas, notably the development of more convenient, patient-centric dosage forms. The evolving science behind ODF production provides a useful case study, demonstrating both the challenges drug manufacturers must overcome to better serve young patients, and the incredible potential these treatments represent.

THE BASICS OF ODF FORMULATION

The vast range of biocompatible polymers available and advancements in thin-film technologies has made it possible to develop a variety of ODF formats since the first prescribed ODF in 2010 – fuelling their acceptance and popularity as a novel drug delivery system. Although ODFs can take many different forms, in the pharmaceutical industry, they typically appear in a 2 x 3 cm strip, weighing 30–40 mg and loaded with 20–30 mg of API. Buccal and sublingual mucosa applications have gained the most interest in recent years, but ODFs can be delivered via ocular and transdermal routes too.

When it comes to suitable actives, ODF formats are most compatible with relatively potent, water-soluble and ethanol-soluble APIs that can be dosed at less than 30 mg/day. Relevant applications include prescription and over-the-counter product groups, including cough, cold, sore throat, allergic reactions, gastrointestinal, pain and sleep medications. ODF forms are also an ideal choice for the delivery of substances susceptible to first-pass metabolism. Nano/micronised Biopharmaceutics Classification System (BCS) class II and IV drugs and biomolecules have recently been identified as suitable candidates for ODF formulation too, enabling a more patient-friendly alternative for some APIs that are traditionally delivered via parenteral delivery routes.

At base-line level, ODF formulations require a film-forming polymer or combination of polymers, such as maltodextrin, hydroxypropylated starch, hydroxypropyl methylcellulose (HPMC), gelatin or hydroxypropyl-beta-cyclodextrin (HPβCD), a plasticiser such as sorbitol or glycerol, a surfactant, a sweetening and flavouring agent, and – depending on the specific application – a saliva-stimulating agent.

There are a number of viable manufacturing options for ODFs, but the most commonly used processes include solvent and semi-solid casting, hot-melt extrusion, solid dispersion and rolling. And the mechanical strength, muco-adhesive properties and drug-release rate of the formulation can be adjusted by using different combinations of polymers in different amounts. All this apparent flexibility makes it difficult to understand why ODFs remain relatively uncommon in paediatric healthcare (Figure 2) but, as with all pharmaceutical dosage forms, there are caveats that put a damper on their mainstream viability.

"Manufacturers must consider disintegration time, textural properties, API stability, taste and mouthfeel – all while keeping the number of ingredients to a minimum to reduce production complexity."

Figure 2: ODFs have immense potential to improve paediatric drug delivery but are currently uncommon in paediatric healthcare.

A QUESTION OF STABILITY

In ODF formulations, balance is critical. To create a successful end product, manufacturers must consider disintegration time, textural properties, API stability, taste and mouthfeel – all while keeping the number of ingredients to a minimum to reduce production complexity. Drug producers can call upon several pre-processing strategies to help increase API solubility and bioavailability in ODFs, the most common of which are API treatments, including micronisation or nanonisation. However, even with these steps, preserving the physical stability of poorly soluble APIs in ODFs remains a ubiquitous challenge.

Research conducted by scientists at Roquette Pharma Solutions set out to explore this issue and evaluate whether the excipient HPβCD could support the formulation stability of an ODF featuring the poorly water-soluble model drug loratadine.[6] In the trial, ODFs were prepared using HβCD as the bulk filler excipient and the long-chain polymer HPMC 60HD50 was included to further enhance the film's mechanical properties. Suitable plasticisers were also included. HPβCD was not included in the control ODF formulation. The ODFs were prepared via two different production methods; an ethanol/aqueous (60:40) co-solvent system; or a solvent-free process involving heat-cool-heat cycling (121°C, 1 atm).

The chemical stability of the loratadine ingredient was evaluated following its heat-cool-heat production cycle via reversed-phase high-performance liquid chromatography (RP-HPLC) with ultraviolet (UV) light and charged aerosol detectors (CADs). The final ODF formulation was assessed according to critical quality attributes, including disintegration time, mechanical properties, moisture content and taste masking. Solid-state characterisation was conducted via polarising light microscopy (PLM), X-ray diffraction (XRD) and differential scanning calorimetry (DSC).

When comparing the two formulations, researchers found that the HPMC-only loratadine films initially presented as amorphous solid dispersions but underwent significant drug recrystallisation after one week of storage in a closed polyethylene bag at ambient conditions. In contrast, minimal drug recrystallisation was detected in the loratadine films formulated with HPβCD. The study also found that inclusion of HPβCD in the formulation increased the aqueous solubility of loratadine and helped suppress the bitter taste of the drug in a concentration-dependent manner.

Based on these findings, the Roquette research team concluded that using HPβCD as the primary excipient in an ODF formulation successfully conferred the properties of solubility enhancement and taste masking, while helping to assure the physical and chemical stability of the drug. These results represent a positive development for manufacturers of paediatric medications, providing a useful starting point for further investigation.

"Market commentators speculate that 3D printing could unlock "build-your-own" medications for patients."

THE POTENTIAL OF 3D PRINTED ODFS

As we have seen, smart excipient selection, complexation and formulation strategies already exist for maximising the effectiveness of ODFs. Looking ahead, however, the world of alternative paediatric dosage forms is taking on a new dimension. Having simmered close to the surface for almost 20 years, the pharma industry is seriously considering 3D printing as a valuable tool for increasing access to more convenient dosage formats. There is still work to be done here regarding standardised protocols for processing safety, but the future generally seems bright for 3D-printed pharmaceuticals – particularly for paediatrics.

The benefits offered by this technology fall into two main categories: patient centred and manufacturing centred. In the case of the former, market commentators speculate that 3D printing could unlock "build-your-own" medications for patients, similar to the 3D printed, customisable supplements already popular in the nutraceuticals sector.[7,8,9] On the manufacturing side, the key advantages are speed and flexibility. 3D printing has the potential to significantly reduce time to prototype, empowering manufacturers to accelerate the path to clinical testing while keeping development costs low.[10] These features are especially relevant in the context of devising specific treatments for children, the lower demand for which made them an unattractive candidate for time- and cost-intensive traditional manufacturing methods.

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SOLUBILITY IMPROVEMENT ENTERS A NEW DIMENSION

3D printing could represent the next great leap in solubility improvement for ODF formulations, too. In a recent study, researchers at Roquette explored the viability of a 3D-printed ODF formulation containing loratadine as the API and HPβCD as a solubilising and filler excipient.[11] The specific objective of this study was to optimise an ODF formulation of a poorly soluble drug for 3D printing, using the pressure-assisted microsyringe technology, also known as bioprinting.

Building on the previous research presented at AAPS PharmSci360 in 2020, an HPβCD-HPMC-loratadine formulation was selected for the study. The prepared hydrogel demonstrated shear thinning properties with slight thixotropy, which allowed it to be successfully extruded from the syringe tip and recover its shape immediately after printing. Researchers were able to achieve the required amorphous state for the loratadine API through complexation with HPβCD. This complexation step was critical to ensuring the poorly soluble active could be incorporated into the ODF in a sufficiently high concentration to be effective.

Upon its conclusion, the study successfully demonstrated that a hydrogel formulation consisting of HPβCD, sorbitol and HPMC was suitable for the fabrication of ODFs via 3D printing by the pressure-assisted microsyringe technology. In addition, it provided further evidence of HPβCD's value as a solubility enhancer in ODF formulations and established a workable set of printing parameters for optimised ODF formulation through 3D printing. The implications of having a fast, effective and cost-efficient method for producing patient-centric dosage forms are extremely significant, not just for children's medicine, but for treatment of any patient group with specialised dosage requirements.

FILMS OF THE FUTURE

ODFs are an undeniably powerful weapon in the fight for better paediatric pharmaceuticals. The studies mentioned in this article, and many more besides, have produced some incredibly positive results that will begin to turn the tide on the industry's acceptance of ODFs as a mainstream dosage form – but the conversation cannot end here. More work is needed to tackle the API solubility and stability issues associated with ODF production, and increase awareness among producers, paediatricians and patients alike of the game-changing potential these flexible films represent. With these goals at the forefront, pharma producers can build a brighter future where every patient has access to the specialised care they need – whether young, old or anything in between.

ABOUT THE COMPANY

Roquette is a family-owned global leader in plant-based ingredients, a pioneer of plant proteins and a leading provider of pharmaceutical excipients. Founded in 1933, the company currently operates in more than 100 countries, has a turnover of about €5 billion (£4.3 billion) and employs more than 8,000 people worldwide. Life and nature have been its sources of inspiration for decades. All its raw materials are of natural origin. From them, the company enables a whole new plant protein cuisine; it offers pharmaceutical solutions that play a key role in medical treatments; and it develops innovative ingredients for food, nutrition and health markets. Roquette aims to unlock the potential of nature to improve and save lives. Thanks to a constant drive for innovation and a long-term vision, the company is committed to improving the wellbeing of people all over the world. It puts sustainable development at the heart of its concerns, while taking care of resources and territories. The company is determined to create a better and healthier future for all generations.

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Keat Theng Chow, PhD, heads the Applied Sciences Pharma team at the Asia Pacific Innovation Center at Roquette. Tasked to deliver the innovation pipeline for its Pharma Solutions business, she and her team support the strategic management of Roquette's innovation portfolio and oversee the operations management for the Asia Pacific Innovation Center located in Singapore. Dr Chow joined Roquette in 2017 as a Pharmaceutical Research Manager following 10 years of experience working in pharmaceutical product development with Abbott, AbbVie, MSD and A*Star. She holds a BSc in Pharmacy and a PhD in Pharmaceutics from the National University of Singapore, after which she completed her postdoctoral fellowship at The University of Texas in Austin (US) in 2009.

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