NOVEL ORAL DELIVERY SYSTEMS

ON drugDELIVERY

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NOVEL ORAL DELIVERY SYSTEMS

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Front cover image, EUDRATEC™ PEP modular oral delivery system for biomolecules", supplied by Evonik Nutrition & Care GmbH. Reproduced with kind permission.

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SELECTING OPTIMAL FORMULATION TECHNOLOGY FOR BETTER PATIENT TREATMENT

In this article, with a focus on lipid-based formulations, Stephen Tindal, Director, Scientific Affairs, Catalent Pharma Solutions, provides insights into Catalent's strategies for oral formulation selection which can lower attrition rates, and therefore development costs and time to market.

Drug development is an expensive business. With the average cost of bringing a molecule from idea to marketplace put at more than US$2.6 billion (£2 billion) by the Tufts Center for the Study of Drug Development (Boston, MA, US),[1] innovative strategies that can speed up this journey by reducing product development cycles are much needed.

There are many areas where innovative strategies can be advantageous, but one of the most important is in the drug formulation area. One such strategy is to identify compounds that are likely to present development challenges such as poor solubility or poor permeability, or both, and apply an appropriate bioavailability-enhancing formulation technology early in development. Given the number of these enabling technologies available, it is important that the formulator select a technology during preclinical development that is most likely to provide optimal delivery of the drug in a format that is most likely to result in patient compliance. Catalent's recommended strategy for achieving this is by employing parallel screening of the various enabling technology options while the molecule is still in the preclinical pipeline. By choosing the right option early – and rejecting those that are unlikely to make it through the later stages of development with the ultimate goal of obtaining regulatory approval – the notoriously high attrition rates that are common can often be reduced,[2] and low productivity rates might be increased.[3]

The Biopharmaceutics Classification System (BCS) has proven valuable in providing a system by which compounds can be grouped into one of four classifications based on the compound's dose, solubility, and permeability.[4] Many of the challenges arising in formulation result from the fact that about two-thirds of all small molecules in current development pipelines fall into Class II of the BCS – those that have poor solubility but reasonable permeability. These poorly soluble compounds tend to have poor bioavailability including reduced absorption, variable (nonlinear) pharmacokinetics and, often, significant food effects.

> "Butler and Dressman devised an alternative, the "Developability Classification System" (DCS).[5] This provides an additional level of granularity to BCS Class II compounds."

Selection of a suboptimal formulation approach can result in patient drug exposure outside of the desired therapeutic range, i.e., levels of absorption too low for the therapeutic effect, or too high, with the occurrence of side-effects and associated toxicity implications. The food effect that often accompanies BCS II compounds is particularly pernicious, as drug absorption will vary considerably depending on whether or not the patient's stomach is empty and the nature of what they have eaten. This poses significant patient compliance issues and in many cases safety or toxicity concerns.

The BCS provides minimal insight into formulation strategies that should be considered based upon a drug's classification. It was instead designed as a regulatory aid identifying those compounds (BCS I) that would not require bioequivalence studies based on their dose, solubility and permeability. As such, it is of limited value for formulators,

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"The soft capsule continues to be the dosage form of choice for the oral delivery of lipid-based formulations and in large part has been responsible for the majority of successful drug products utilising lipid technology on the market."

especially when it comes to determining the right formulation approach(es) for the problematic Class II compounds. As a result, Butler and Dressman devised an alternative, the "Developability Classification System" (DCS).[5] This provides an additional level of granularity to BCS Class II compounds that are poorly soluble by identifying drugs that are dissolution-rate limited (DCS Class IIa), and those drugs that are solubility-limited (Class IIb). This further differentiation of a drug's poor solubility behaviour (dissolution-rate limited *versus* solubility-limited) is useful in identifying the proper choice of formulation strategy at an early stage of development.

This is important because in recent years a number of solubility-enabling formulation technologies have been employed that permit poorly soluble compounds to be successfully formulated into drug products. These widely used technologies include particle-size reduction, solid amorphous dispersions, and lipid-based formulations. The placement of a compound in DCS IIa or IIb facilitates the proper selection of a formulation strategy based upon the compound's solubility characteristics.[5] While computer-based prediction tools can assist in the selection of a formulation strategy, there remains no substitute for preformulation studies in the lab followed by the development of prototype formulations incorporating proposed formulation approaches, and their subsequent PK testing in animals and humans. The parallel screening of multiple formulation approaches during the preclinical stages of development (or, at the latest, in the early stages of clinical development), increases the probability of achieving acceptable efficacy while addressing potential safety concerns. This results in faster development timelines, and reduced attrition rates for new chemical entities.

LIPID-BASED DELIVERY

Lipid-based drug delivery systems have been employed successfully for challenging compounds with poor solubility for many years. Enhanced bioavailability is a result of the development of lipid formulations that initially solubilise the compound prior to administration and maintain the drug in solution as it travels the gastrointestinal tract. During development, often the dispersion and digestion properties of lipid formulations are studied *in vitro* as a means of predicting the formulation's behaviour *in vivo*.[6,7]

Lipid-based formulations are classified according to the lipid formulation classification system (LFCS). This system was proposed in 2006 and initially classified lipid-based formulations into four different categories (Type I – IIIB),[8] with a fifth category (Type IV), being added a year later (see Table 1).[9]

Drug product	Characteristics	Excipients in formulation Content of formulation (%w/w)			
		Oils: triglycerides or mixed mono and diglycerides	Water-insoluble surfactants (HLB < 12)	Water-soluble surfactants (HLB > 12)	Hydrophilic cosolvents (e.g. PEG, proylene glycol, transcutol)
Type I	• Pure oils • Limited or no dispersion • Digestion required	100	-	-	-
Type II	• SEDDS • Moderate dispersion needed to form an emulsion • Likely to require digestion	40-80	20-60	-	-
Type IIIA	• SMEDDS • Rapid dispersion to form micro- or nano-emulsion • May need digestion	40-80	-	20-40	0-40
Type IIIB	• SMEDDS • Rapid dispersion to form micro- or nano-emulsion • Digestion likely not needed	<20	-	20-50	20-50
Type IV	• Oil free • Rapid dispersion results in micellar solution • No digestion needed	-	0-20	30-80	0-50

Table 1: Lipid formulation classification system.[8,9]

The formulations are assigned to a category based on the types and amounts of excipients, and predicted behaviour (characteristics) *in vivo*. Type I lipid formulations are pure oils and require digestion whereas Type IV lipid formulations do not contain oils and rapidly disperse into micelles.

> "Not only have these non-gelatin soft capsules found wide application and appeal to the vegetarian segment of consumers, but the shells have found a number of new pharma applications owing to the expanded range of lipid fill formulations that can now be encapsulated into soft capsules."

A comprehensive screening process should be used to determine the optimal excipient and ratio for each individual compound, and it is possible to speed up this process if parallel studies are carried out.

Parameters that should be considered during the screen include the solubility of the drug in the different excipients, media and lipid digestion products, the compatibility of the excipients, whether the API is prone to degradation, and how likely the API is to precipitate out on dispersion and digestion.

The soft capsule (Figure 1) has been, and continues to be, the dosage form of choice for the oral delivery of lipid-based formulations and in large part has been responsible for the majority of successful drug products utilising lipid technology on the market.[10] The reasons for this are: 1) most lipid formulations as well as the excipients making them up are liquid in nature, or semi-solids with low melting points; 2) the vast majority of lipid excipients, surfactants, and cosolvents comprising lipid-based fills are compatible with the soft capsule shell given the formulator's ability to tailor the shell composition to a specific fill formulation; 3) properly formulated soft capsule shells rupture and dissolve quickly once administered thereby allowing rapid release of the lipid-based fill and its uncompromised performance (dispersion and digestion) in the gastrointestinal tract; and 4) process parameters established on a small scale in the lab and pilot plant are readily scalable to a robust commercial scale manufacturing process, in contrast to many other dosage forms.

Other advantages offered by the soft capsules include:[10] 1) utilisation for highly potent drug compounds, often microgram doses, where uniformity of dose is best achieved by precisely dosing the fill solution of the drug into the soft capsule; 2) minimisation of safety concerns associated with dusty operations for conventional solid dose manufacture given the drug is wetted early in the soft capsule manufacturing process; and 3) coupled with closed manufacturing processes, the soft capsule provides excellent protection for those APIs that are oxygen sensitive as it is hermetically sealed with no headspace and the shell of the soft capsules generally exhibits very low oxygen transmission rates.

It has been well established that lipid-based formulations filled into soft capsules and engineered to release the fill immediately upon administration and spontaneously disperse to form fine, thermodynamically stable emulsions, often enhance the bioavailability of poorly soluble (DCS II) compounds. This can result in improved absorption, or a reduction in the variability of that absorption. More recently, in addition to immediate-release applications, the filling of lipid semi-solid formulations into soft capsules has been used for extending the release of DCS II drugs.[11] Targeted release of lipid-based fills containing API can also be accomplished through the application of functional film coatings (for example, enteric coatings) to the soft capsule.

The conventional softgel utilises a gelatin-based shell but, more recently, alternative shells containing plant polysaccharides as a replacement for gelatin have been developed. Not only have these non-gelatin soft capsules found wide application and appeal to the vegetarian segment of consumers, but the shells have found a number of new pharma applications owing to the expanded range of lipid fill formulations that can now be encapsulated into soft capsules. These include higher melting point fills that can be heated to temperatures not possible with a gelatin-based shell, thereby allowing encapsulation of very viscous liquids and semi-solid fills as well as improved shell compatibility with a number of medium chain fatty acids, surfactants and cosolvents.

In addition to the technical applications described above, soft capsules are believed to have gained wide acceptance by patients

Figure 1: The soft capsule continues to be the dosage form of choice for the oral delivery of lipid-based formulations.

> "It has never been more important to determine the optimal delivery form at an early stage. Many of these challenging molecules could have significant benefits for patients, yet if they cannot be successfully delivered then that potential will never be realised."

Drug	DCS	Formulation	F (%)	PK Variability (coefficient of variation, CV%)[13,14]	Food Effect	Drug-Drug Interactions		
						Substrate	Inhibitor	Inducer
Abiraterone acetate	Class IIb	Tablet	50%	Relative bioavailability for the modified fasting state Inter-subject 61.1% Intra-subject 71.3%	• Formulation in olive oil increased exposure 4.5-fold • 2-4.4 fold increase in exposure when administered with high-fat meal to cancer patients • Recommended to take under fasting conditions	CYP3A4 (minor) SULT2A1 (major)	CYP2D6 (strong) CYP2C8 (moderate) CYP1A2 (weak) CYP2C8 (weak)	

Table 2: Profile of abiraterone acetate.

and consumers. This is clearly evidenced in the consumer healthcare products area where many dietary supplements, such as omega-3 oils, are available in the soft capsule format. These products are easier to swallow than tablets and provide odour-masking of the fill contents making for a more positive consumer experience. The impact of soft capsules in another consumer product category, painkillers, has also been significant, where solutions of API have resulted in a faster onset of action, which is advantageous for consumers seeking fast relief.[12]

The drug abiraterone acetate represents a good example of a drug product that is marketed in a conventional dosage form (tablet) that may have benefited from the use of a lipid-based drug delivery system. Abiraterone acetate is a steroidal antiandrogen drug that is prescribed for the treatment of metastatic castration-resistant prostate cancer, dosed along with the steroid drug prednisone, and acts by inhibiting the body's synthesis of ligands that bind to the androgen receptors. It is given as a once-daily oral dose.

This compound falls into DCS Class IIb, given that its lack of solubility is due to its poor intrinsic solubility. Labelling for the marketed dose form indicates a significant positive food effect and it is recommended to be taken on an empty stomach. This raises serious safety concerns if patients do not follow labelled instructions, which in all likelihood will result in increased and variable absorption

Based on its DCS classification (IIb), this compound may have been better developed using a solubilisation-enabling technology. The increased exposure observed when formulated with olive oil or co-administration with a high-fat meal would suggest that a lipid-based formulation approach may have resulted in improved and less variable absorption.

CONCLUSION

Lipid-based drug delivery systems are well established in the market, and a proven technology for enhancing the bioavailability of poorly soluble compounds. Yet there are many instances where this technology is not considered during development and drugs that would have benefited from its use have instead been developed in suboptimal dosage forms. With the increasing number of drugs in the development pipeline that are poorly soluble, poorly permeable, or both, it has never been more important to determine the optimal delivery form at an early stage.

Many of these challenging molecules could have significant benefits for patients, yet if they cannot be successfully delivered then that potential will never be realised. To accomplish this most successfully, it is therefore important to carry out parallel screening of bioavailability-enhancing technologies at an early stage by in-house formulation experts, or to seek assistance from a reputable, quality CRO that has the expertise to perform this work.

Regardless of whether a lipid-based formulation, or another technology is selected as the right formulation approach based on the API's physicochemical properties, doing so at the early stages of development will reduce overall development cycle times and, most importantly, improve patient outcomes.

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ABOUT THE AUTHOR

Stephen Tindal, Director, Scientific Affairs, is based at Catalent's Somerset, NJ, R&D facility and has nearly 30 years of experience in softgel formulation. He has wide expertise in commercializing many Rx, Gx, OTC and VMS products. His current role sees him supporting customers in applying softgel technologies to overcome specific API challenges. Mr Tindal holds a BSc in Chemistry and Analytical Science from Loughborough University, UK, and is a member of the Catalent Applied Drug Delivery Institute.

AN INNOVATIVE SMART ORAL DELIVERY TECHNOLOGY FOR PROTEINS AND PEPTIDES

Andrea Engel, PhD, Head of Particle Formulation Laboratory; Anne Benedikt, PhD, Head of Biopharmaceutical Laboratory; and Hans Baer, MSc, Senior Project Manager, all of Evonik, explain how their recently introduced new modular platform technology for improving the oral bioavailability of peptides may offer a feasible solution to the problem of compliance with peptide drugs. These can be highly beneficial for conditions such as diabetes, oncology and metabolic disorders but the fact they have to be delivered as injections has limited their appeal, a problem which may be solved by technology that enables it to be used as a tablet.

During the last few decades the use of therapeutic proteins and peptides for applications in medicine and biotechnology has gained high interest. Peptide drugs can be highly beneficial in major diseases such as diabetes, oncology and metabolic disorders. The global peptide market is expected to increase up to US$25.4 billion (£19.2 billion) in 2018.[1] Therapeutic peptides in general are known to be highly selective, efficacious, safe and well tolerated.

For patients and medical practitioners alike, compliance is often a determining factor in the choice of medication. It has a significant impact on how widely a drug is prescribed. A study revealed patients' preferences for different routes of administration, showing the majority of patients preferred daily tablets over monthly injections.[2] Nevertheless, various formulation approaches for oral protein and peptide delivery considered in the last decades have not constituted the desired breakthrough.[3]

> "Patients receiving protein and peptide injections often experience discomfort and pain, which results in an overall inconvenient therapy concept."

Most pharmaceutical proteins and peptides are considered to be BCS Class III drugs, thus having a good solubility but poor permeability, which leads to an overall poor bioavailability. Furthermore, poor stability and short plasma half-life are major drawbacks. Therefore, most of the protein and peptide drugs in the market today are administered parenterally as injections. Patients receiving protein and peptide injections often experience discomfort and pain, which results in an overall inconvenient therapy concept.

In order to offer a feasible solution, Evonik recently introduced a new modular platform technology for improving the bioavailability of peptides. Evonik's EUDRATEC™ PEP technology allows treatment in capsule form, replacing unpleasant injections and therefore tremendously enhancing patient compliance. The technology provides all the advantages

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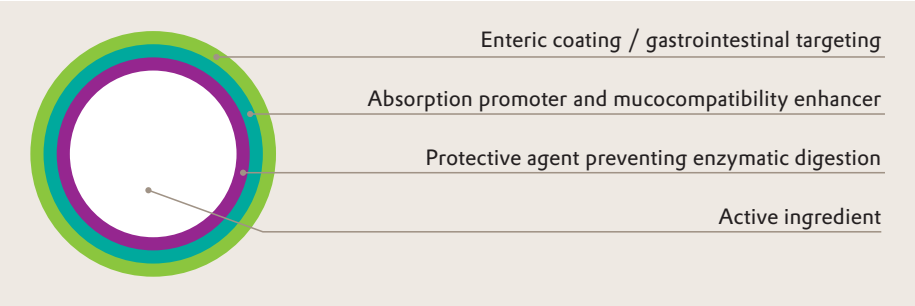


Figure 1: Typical EUDRATEC™ PEP particle design.

of oral solid dosage forms for poorly permeable active pharmaceutical ingredients such as, but not limited to, proteins and peptides. Due to its modular approach, the finished dosage form can be tailored to the drug's special needs.

EUDRATEC™ PEP TECHNOLOGY

Various aspects have to be considered during formulation development including the stability, solubility and permeability of proteins and peptides, the site of absorption and the compatibility with the mucus. The innovative EUDRATEC™ PEP technology is a modular multiparticulate platform technology.

The formulation approach uses conventional oral solid dosage form manufacturing technologies and can therefore be integrated easily in existing manufacturing concepts. The drug products are formulated on the basis of either microparticles or mini-pellets, wherein the particles contain various thoroughly selected modules of the EUDRATEC™ PEP system that are required for the specific active.

Several synergistic modules include the active ingredient, a permeation promotor, a bioavailability promoting agent and a polymeric coating for the gastrointestinal targeted release. Depending on the type of active ingredient, additional modules can be applied to achieve further customised and beneficial functionalities. Each particle is essentially a complete pharmaceutical system, typically comprised of four basic modules (Figure 1).

The following standard modules are applied:

- Gastrointestinal targeting
- Absorption promotor
- Enzymatic protection
- Mucocompatibility.

The following advanced modules can be applied additionally:

- Anti-aggregate
- Release control
- Active ingredient specific components, e.g. stabiliser.

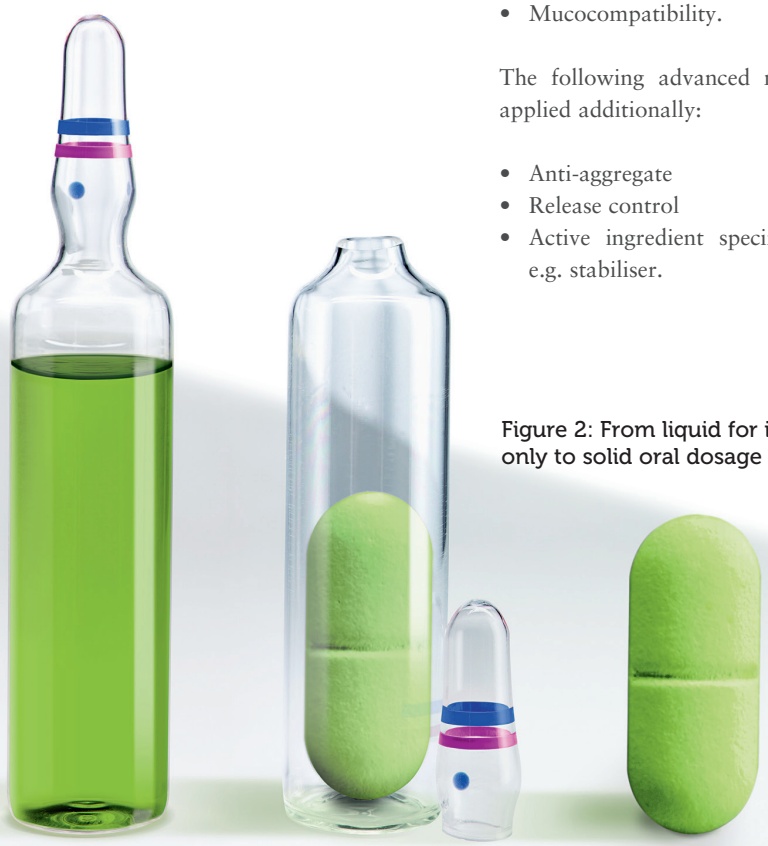


Figure 2: From liquid for injection only to solid oral dosage form.

THE MODULES AT A GLANCE

Up to now, parenteral administration remains the most common application route for therapeutic macromolecular active ingredients like proteins and peptides due to their poor oral bioavailability. However, considering patient acceptance and long-term compliance, the oral administration route is preferred, resulting in an increase in the therapeutic value of the drug. The formulation of proteins and peptides as oral dosage forms requires advanced drug delivery strategies to overcome physiological challenges of the gastrointestinal tract, including enzymatic degradation, poor permeability and large molecular size [4] and thus ensuring proper bioavailability (Figure 2).

Gastrointestinal Targeting

Proteins and peptides require protection from the gastric fluid to avoid degradation induced by the stomach's acidic environment. When entering the upper small intestine, the environmental pH increases and the protective functionality shall disappear. Such functionalities are offered by commonly used enteric coatings. Over more than 60 years, anionic EUDRAGIT® polymers have been the industry standard for delayed-release coatings, preventing the release of the active pharmaceutical ingredient in the stomach. The poly(meth)acrylate chemistry behind EUDRAGIT® polymer systems provides an exceptionally versatile platform for designing drug delivery to match the specifics of individual pharmaceutical actives and treatments. The polymers used in EUDRATEC™ PEP are impervious to the stomach's acidic environment, but dissolve rapidly at specific higher pH values.

Absorption Promotor

The absorption of proteins and peptides is very limited due to their size and the intestinal barrier. An absorption promoter mediates enhanced permeation over the intestinal barrier via the paracellular pathway. The efficacy of penetration enhancers depends on several factors, including peptide type, nature of the enhancer, physicochemical properties of the delivery system as related to the drug release, and the site of application. In order to provide a successful concept, the enhancer must be released either simultaneously with or shortly before the peptide.[5] Several absorption enhancers are discussed in the literature, but a key aspect of absorption promotors is to act reversibly and without persistent impairment.

Enzymatic Protection

One of the main obstacles limiting oral bioavailability of proteins and peptides is caused by luminal or brush border membrane-bound proteolytic enzymes such as pepsin, trypsin, chymotrypsin and pancreatin, leading to a severe pre-systemic degradation in the gastrointestinal tract. An enzymatic inhibitor has to be selected for peptide protection from proteases. It is dependent on the amino acid composition and on the position of the amino acids within the active peptide as well as the pH value.[6]

Mucocompatibility

The luminal surface of the intestinal membrane is covered by a layer of mucus which effectively protects the epithelial surfaces. Excipients interfering with mucus can increase the residence time at certain absorption windows. Such local increases in combination with high concentrations of proteins and peptides generate a favourable diffusion gradient to support the permeation through the mucus barrier.

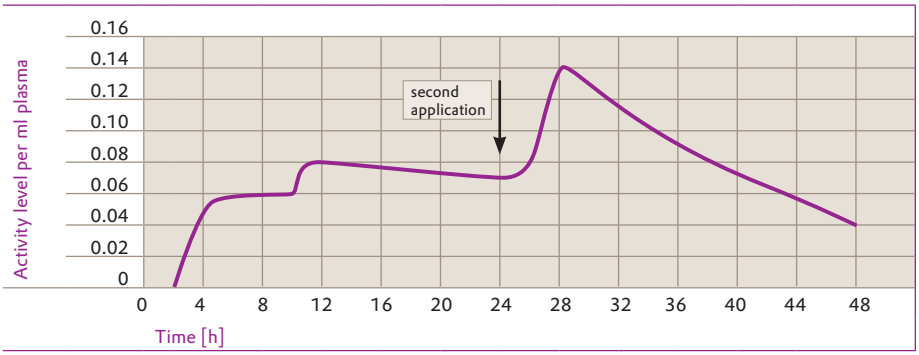
Multiparticulate Dosage Form

In EUDRATEC™ PEP formulations, the therapeutic dose is distributed over a large number of particles which are assembled into a capsule as a multi-unit dosage form. The final dosage forms are manufactured by using polymers and materials that are physiologically safe in conventional production processes, and can also be used in GMP compliant production processes.

BIOAVAILABILITY ENHANCEMENT PROVEN IN VIVO

Several *in vivo* studies emphasise the therapeutic benefits of the EUDRATEC™ PEP technology. It was applied for an anionic glycosidic drug which does not show any oral bioavailability when used unformulated. The drug is typically administered parenterally. A study in monkeys revealed that the activity of the drug could be measured in plasma. Furthermore, very promising pharmacokinetics providing a prolonged and adjustable plasma profile could be obtained through repeated application (Figure 3).

In addition to that the EUDRATEC™ PEP system was used to enhance the bioavailability of a commercially available oral peptide formulation. The technology led to a seven-fold increase of relative bioavailability of the peptide in a mini-pig cross-over study compared to the conventional tablet (Figure 4).



oral reference is not shown since the profile is on 0-level

Figure 3: EUDRATEC™ PEP mean activity profile in a monkey study (n=3), second application after 24 hours.

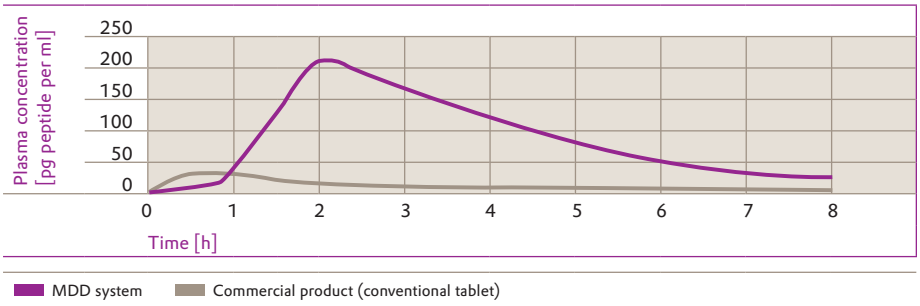


Figure 4: Mean plasma profiles in a mini-pig cross-over study (n=8).

> "Overall, Evonik's proprietary EUDRATEC™ PEP smart formulation toolbox for oral administration of macromolecular active pharmaceutical ingredients provides a unique concept for tailor-made drug delivery profiles."

BENEFITS OF EUDRATEC™ PEP

As a modular, multiparticulate platform technology, customised functionalities can be achieved successfully. EUDRATEC™ PEP formulations increase the oral bioavailability of proteins and peptides as well as other small and medium-sized biopharmaceuticals. The system enables parenterally administered medicines to be replaced by oral dosage forms. *In vivo* studies confirmed the suitability to enhance the bioavailability of drugs and the safety advantage of the system *versus* parenteral formulations.

Evonik's absorption enhancers were well tolerated in animal studies. EUDRATEC™ PEP formulations have shown superior results in pig and monkey studies employing a peptide drug and an anionic glycoside drug, respectively.

As a technology provider, Evonik offers a well-designed concept for the customised formulation development, starting with the selection of suitable EUDRATEC™ PEP modules and materials based on the physicochemical characteristics of the protein or peptide used. The chosen modules and materials are then evaluated within a systematic compatibility study.

Followed by the manufacturing of first preclinical prototypes, Evonik performs standardised *in vitro* characterisation of the prototypes employing compendia test methods. Besides pharmacopoeial dissolution test methods, investigations with bio-relevant media are a core competency of Evonik. In addition, biopharmaceutical *in vitro* assays, such as the well-established Caco-2 transport assay, are performed in order to gain first indications of the drug transport across the intestinal barrier. After a successful prototype screening, Evonik can provide samples for preclinical studies and clinical development.

Overall, Evonik's EUDRATEC™ PEP smart formulation toolbox for oral administration of macromolecular active pharmaceutical ingredients provides a unique concept for tailor-made drug delivery profiles.

THE FUTURE

EUDRATEC™ PEP provides valuable opportunities for the lifecycle management of parenteral protein and peptide formulations. The unique technology generates advanced pharmacokinetics and economic advantages compared with conventional oral formulation concepts by significantly reducing the quantity of drug required and thus lowering product costs. Compliance is significantly improved thus increasing the therapeutic success of the specific protein or peptide.

ABOUT EVONIK

Evonik, the creative industrial group from Germany, is a world leader in specialty chemicals, operating in the Nutrition & Care, Resource Efficiency and Performance Materials segments. The company benefits from its innovative prowess and integrated technology platforms. In 2015 more than 33,500 employees generated sales of around €13.5 billion and an operating profit (adjusted EBITDA) of about €2.47 billion. The Nutrition & Care segment is a strategic partner for producers of pharmaceuticals, nutritional supplements and medical products. Its Health Care business line provides a wide range of functional pharmaceutical excipients, drug delivery technologies, development services, and GMP manufacturing for oral and parenteral formulations.

The EUDRATEC™ portfolio of proprietary technologies for oral targeted drug delivery systems enables specific release profiles tailored to medical needs and drug requirements and thus provides smart formulation solutions for value added therapies.

ABOUT THE AUTHORS

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TRANSDERMAL. MARKETLEADER.

ORAL THIN FILMS – REALMS OF POSSIBILITY?

As interest in oral thin film grows, there is an increasing effort to study new and improved methods of drug delivery in the buccal cavity. Muco-adhesive studies have increased, leading to the introduction of a prescription product approved for chronic pain treatment. This article, from Rick Chan, PhD, Executive Scientific Officer, LTS Lohmann Therapy Systems, will discuss the fundamentals of transmucosal absorption and how formulation effort and the drug properties influence drug absorption in the buccal cavity.

The oral route of drug administration is the most common and offers the significant benefits of being non-invasive, and pain avoidance. Increasingly, there is an interest in transmucosal delivery via the buccal cavity. The sublingual route of administration has been used for decades to deliver glyceryl trinitrate for the treatment of angina. A key advantage of a drug delivered transmucosally in the buccal cavity is the avoidance of first-pass metabolism and consequent increase in bioavailability. Correspondingly, this increase in bioavailability could lead to a lower dose requirement and hence reduce drug exposure and associated side effects.

In addition, oral thin films are typically fast dissolving, negating the need for water when administered. This eliminates the fear of choking associated with swallowing a tablet or for people suffering from dysphagia, difficulty swallowing. They therefore offer significant benefits to patient populations such as the elderly or those suffering from parkinsonism.

SITE OF ABSORPTION & TRANSPORT MECHANISM

The major sites of transmucosal absorption are under the tongue and though the buccal cheek and, to a lesser extent, drug absorption takes place in the palate, and the lingual part of the tongue. The lining of the mucosa in these areas is covered by a stratified, non-keratinised squamous epithelium (see Figure 1 and Table 1).[1] Although the surface areas of the oral mucosa are relatively small when compared with the gastrointestinal tract or skin, the high vasculature lends itself to potential drug absorption.

> "For absorption to occur, the API must be dissolved. If the drug is too lipophilic, it cannot dissolve sufficiently in the aqueous medium and hence may not be available for significant absorption. Thus a delicate balance exists between the lipophilicity of the drug and the solubility."

A potential hindrance to drug permeation across the buccal mucosa is the presence of membrane-coating granules (MCGs) which are vesicles observed in the cells composing the epidermis and have been described as the precursors of the keratin layer. It has been reported that some MCGs in the buccal mucosa contain a roughly organised lipid lamellae domain.[2] The intercellular space of this stratified, non-keratinised buccal

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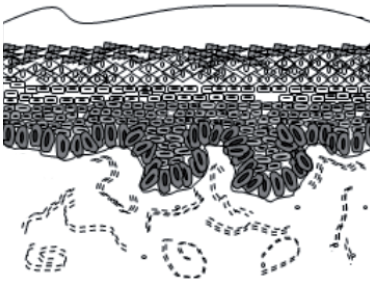
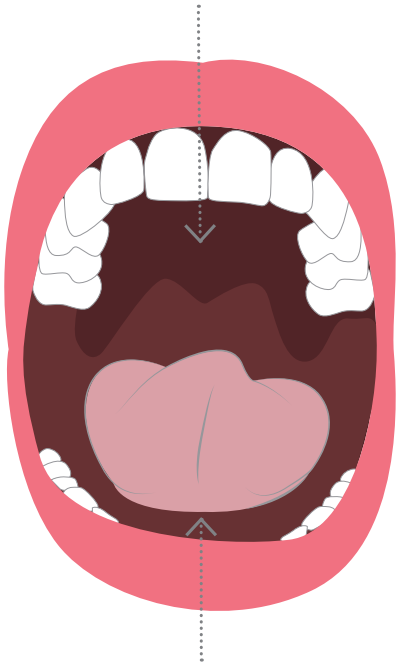


Keratinised mucosa



Non-keratinised mucosa

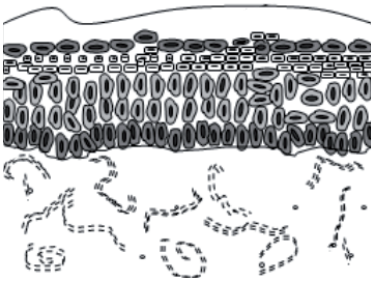


Figure 1: Mucosal regions of the mouth.[1]

Regional variation of mucosal tissue within the oral cavity

Mucosa type	Charcteristics
Masticatory	Keratinized epithelium Hard palate, gingival 25% of total surface area of oral cavity
Lining	Nonkeratinized epithelium Cheek, sublingual, alveolar 60% of total surface area
Specialized	Both keratinized and nonkeratinized Tongue 15% of total surface area

Table 1: Regional variation of mucosal tissue within the oral cavity.[1]

membrane is filled with a combination of amorphous materials where short stacks of lipid lamella can be observed. This structural difference observed in buccal membrane when compared with skin and other keratinised epithelia could be responsible for the difference in permeability of these membranes.[3,4]

The buccal epithelium structure thus contains two different domains, a lipophilic domain corresponding to the membrane of the stratified epithelium; and the more hydrophilic domain corresponding to the extruded content from the MCGs into the inter-cellular space. This then offers two major routes of drug absorption, namely paracellular (between cells) and the transcellular (through cells) pathways (Figure 2).[5]

The lipophilic nature of the cell membranes favours the passage of molecules with high log P values across the cell whereas the polar nature of the intercellular space favours the penetration of more hydrophilic molecules. Depending on the physicochemical characteristics of the drug molecule, either the more hydrophobic, or the more hydrophilic, or a combination of both routes could allow for absorption.[7]

FACTORS AFFECTING DRUG ABSORPTION

Physicochemical Properties of the API

The primary mechanism of drug permeation is via passive diffusion. As a consequence, the partition coefficient, degree of ionisation and the molecular mass exert a major influence on drug delivery across the oral mucosal membrane.[7]

The extent of absorption is generally proportional to the lipophilicity or oil-in-water partitioning of the active pharmaceutical ingredient (API). However, the solubility of the drug also plays a key role.[8] The unionised from of the drug is more lipid soluble, and thus would permeate and diffuse across the biological membrane. The pKa of the drug molecule, and the degree of its ionisation in the pH environment need to be considered for its bioavailability. The effect of pH on drug absorption via the oral mucosa has been studied extensively.[7]

For absorption to occur, the API must be dissolved. If the drug is too lipophilic, it cannot dissolve sufficiently in the aqueous medium and hence may not be available for significant absorption. Thus a delicate balance exists between the lipophilicity of the drug and the solubility. It is therefore important to understand the solubility, pKa of the drug molecule and the pH environment the dosage form is subject to, to maximise drug absorption profile.

Formulation Factors

1. Permeation Enhancers

We discussed earlier that the buccal cavity has limited area for drug absorption, which relies on passive diffusion. This limitation leads to either too small an amount of drug is absorbed or too slow in many cases to exert any therapeutic effects. In order to increase the diffusion of the drug molecule across the membrane, chemical permeation enhancers are commonly used in the formulation to aid absorption.

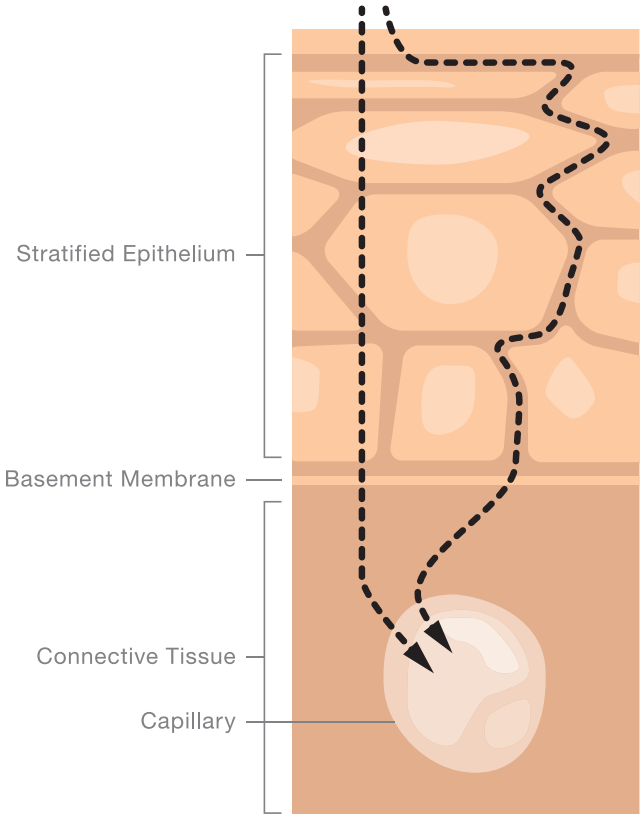


Figure 2: Routes of transepithelial penetration: the transcellular and intracellular pathways.[6]

Permeation enhancers used in transmucosal studies have included surfactants, fatty acids, fatty alcohols, polyols and bile salts.

It has been proposed that permeation enhancers improved mucosal transport in the following ways:[9, 10]

- Changing the mucus rheology in reducing the viscosity and/or elasticity of the mucus layer
- Increasing the membrane fluidity and, in so doing, facilitating transport
- Modifying drug solubility parameters.

Nakane *et al* [11] studied the PK profiles of LHRH released from oral films in dogs. The films were formulated with 5% bile salts, either sodium taurodeoxycholate (STDC), sodium deoxycholate (SDC) and sodium cholate (SC). They observed that the films containing the bile salts released significant amount of LHRH compared with a control film without the bile salt. Higher exposure was obtained for the bile salt with corresponding higher lipophilicity, in the order of sodium dexoxycholate, then sodium cholate and lastly sodium taurodeoxycholate. There was also a corresponding increase in mucosal irritation (Figure 3).

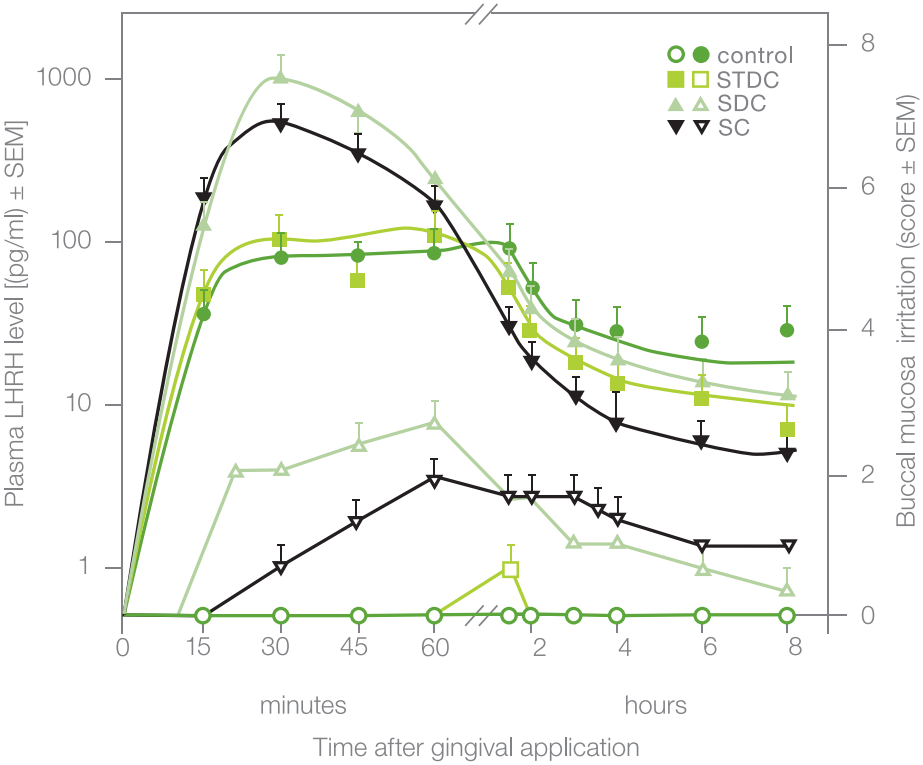


Figure 3: PK profiles of LHRH and buccal mucosal irritation in preclinical study following application of oral thin films containing LHRH 2 mg and 5% bile salt. Closed symbols represent plasma LHRH and open symbols represent buccal mucosal irritation scores.[11]

"Some muco-adhesive films are designed to have a backing layer, akin to that of a transdermal patch, and in so doing, prevent enzymic degradation of the drug and drainage of the drug from the film due to salivary flow."

2. Polymers & Muco-Adhesive Polymers

Oral films are prepared with polymers that form a structure to contain the drug. Many different polymers have been used including cellulose derivatives and gel-forming gums. Cellulosic derivatives include hydroxypropyl methlylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CPC) to name a few, and their choice is dictated by the desired solubility characteristics of the finished film with typically a fast dissolving time being preferred. Although higher-viscosity grades of cellulose have also been used as a means to increase the disintegration time of the film, thus allowing a longer residence time for drug absorption.

Gel-forming gums such as xantham gum, carrageen, and pullulan have been used, mostly in combination with the cellulosic derivatives which impart a greater strength to the film and make them less brittle for handling purposes.

There is an increasing interest in other polymers which possess muco-adhesive properties. Films possessing muco-adhesive properties can adhere to the buccal

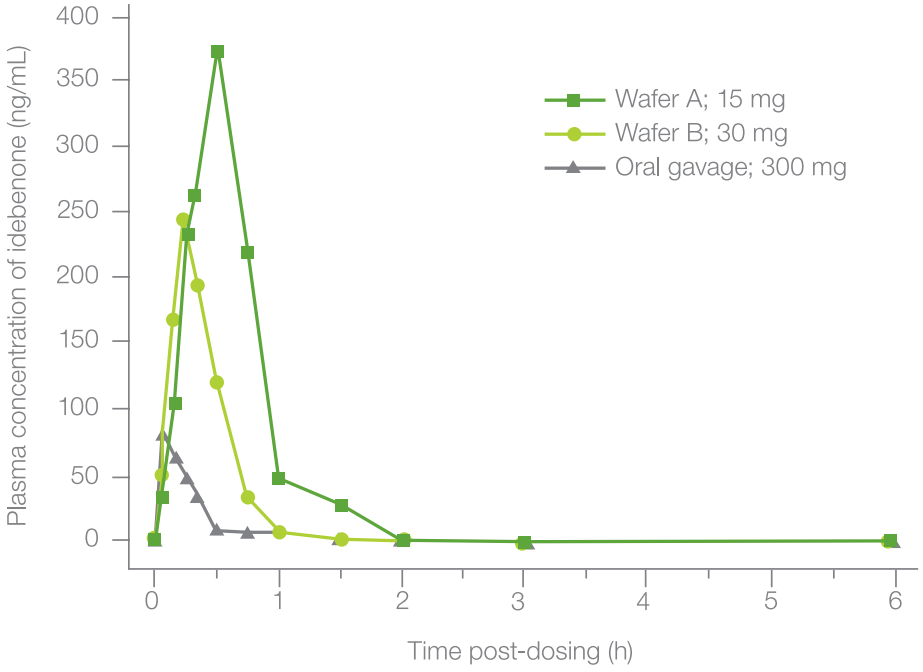


Figure 4: Mean plasma concentrations of free idebenone over time in preclinical study. [14]

mucosa for a prolonged period giving intimate contact. They maintain a high local drug concentration for an extended time for absorption. Some muco-adhesive films are designed to have a backing layer, akin to that of a transdermal patch, and in so doing, prevent enzymic degradation of the drug and drainage of the drug from the film due to salivary flow. Some such polymers used in studies have included polyacrylic acid, chitosan and carbomer.[12, 13]

APPLICATIONS OF ORAL FILM

Fast Dissolving Film with Enhanced Drug Absorption

Oral thin films can dissolve rapidly in the oral cavity and, in some instances, may be absorbed much faster than orally ingested tablets. Especially for drugs which are metabolised extensively by the first-pass effect, an oral thin film formulation provides an opportunity for a faster-acting and better absorption profile. Idebenone is a drug originally developed for Alzheimer's disease. Recently it has been explored for the treatment of a range of neuromuscular diseases. It is well absorbed in the gut but undergoes extensive first-pass metabolism in the liver, leading to a very low bioavailability of less than 5%. The high first-pass effect means that high (multi-gram) doses are required to achieve therapeutic effect, with considerable side effects.

Krumme and Jensen[14] formulated the compounds into oral thin films, one as a suspension (30 mg) and another into a solid solution in which 15 mg of idebenone was dissolved in amorphous form. These films were then administered in a dog study, together with a micro-emulsion (idebenone 300 mg) as a gastric gavage (Figure 4).

The results showed a significant increase in both C_{max} and AUC for the two oral thin film formulations, whereby the 30 mg film achieves three-times the bioavailability, and the 15 mg film achieves five-times bioavailability, compared with that obtained for the microemulsion formulation. When doses were normalised, the suspension formulation showed an improved 26-times bioavailability compared with that of the microemulsion, while the 15 mg solid solution formulation showed an astounding 121-fold improvement! This improvement showed that when the drug is present in amorphous form or in solution, as exemplified by the solid solution formulation, absorption of the drug becomes more complete.

Fast Dissolving versus Muco-adhesive Products: Buprenorphine/Naloxone

While various oral films have been introduced both as prescription only and over-the-counter medicines, buprenorphine + naloxone (BPN/NLX) combination products can be discussed as example to illustrate the different possibilities the oral film offers. For discussion purposes, we focus on the pharmacokinetics of buprenorphine in these products as there were no discernible differences in naloxone PK.

> "To date, most of the applications of oral thin films have been in the delivery of small molecules. With the increasing number of large molecules under development, there has been considerable interest in research to establish if transmucosal delivery is a viable route for administration."

In 2010, Indivior (Slough, UK) received US FDA approval for Suboxone™ (BPN/NLX) oral thin film, which has since become the major product for treatment of opiate addiction, replacing Suboxone sublingual tablet. It has now reached sales exceeding US$1.3 billion (£1 billion) in 2014. In the evaluation document performed by the Australian Therapeutic Goods Administration (TGA),[15] it was concluded that the oral film gave slightly higher exposure parameters when compared with the sublingual tablets in their PK studies. For example, in study 20-250-SA, the C_{max} for Suboxone 2.0/0.5 mg BPN/NLX film is approximately 22% higher compared with the corresponding dose strength of a tablet. Of the different strengths of the Suboxone film, the disintegration times in vivo were measured at from 1-6 min.

Recently, BioDelivery Sciences International (Raleigh, NC, US) introduced Bunavail™ utilising the company's BEMA (bio-erodable muco-adhesive) technology. Patients were instructed to moisten the film and which they then adhered onto the buccal cheek until it completely dissolved.[16] The bioavailability of buprenorphine at various dose strengths was studied and found to be almost double that of the Suboxone tablets.[16]

In Bunavail, the composition is more complex. In the FDA submission review,[17] some of the key points pertaining to buprenorphine absorption from Bunavail are as follow: 4.2/0.7 mg BPN/NLX was found to exhibit equivalent exposure to Suboxone sublingual tablet; and that the co-administration of low or high pH liquid lowered the Cmax and AUC for both actives. Low pH fluid intake caused a greater effect on buprenorphine absorption, with C_{max}, AUC_{last} and AUC_{inf} values being reduced by 59%, 52% and 49% respectively. Higher pH liquid intake reduced the corresponding values by 26%, 24% and 24% respectively. No disclosures were made pertaining to the pH values of the liquids.

While it is difficult to compare the results and outcome from different clinical studies, the two different oral film products seemingly offer very different pharmacokinetics of the absorption of the active ingredients. As there was no disclosure of the detailed formulations of Suboxone sublingual tablets, films or Bunavail film, perusal of pertinent patent/patent applications in the public domain might offer some insight into the difference.

There appeared to be differences in three areas:

- pH of the micro-environment
- Site of administration and
- Residence time.

Myers *et al*[18] disclosed some quantitative data on sublingual film formulations of BPN/NLX and one of the key features claimed was the local pH obtained when the film is dissolved should be 2.0-4.0. For the muco-adhesive film, Finn and Vashist[19] incorporated buprenorphine in a muco-adhesive film and a backing layer, both buffered, to pH 4.0-6.0 and 4.0-4.8, respectively.

Buprenorphine hydrochloride has a pKa value of 8.31.20 In a more acidic environment where the pH is at 2.0-4.0, its solubility increases and thus more molecular moieties become available for absorption. However, in accordance with its dissociation constant, the number of unionised species is considerably less than that at a higher pH. At an environmental pH of 4.0-6.0,

while the solubility of buprenorphine is lower, the number of unionised species is significantly increased when compared with a lower-pH environment. Thus, potentially, more unionised species of buprenorphine are available for absorption. This is supported by the fact that when Bunavail was administered with lower pH liquid, its C_{max} and exposure were reduced. One expects that at higher pH, the C_{max} and AUC values for Bunavail should further increase. This was not the case as it was likely that the solubility of buprenorphine was significantly reduced and hence less drug became available for absorption. This is also an illustration of how delicate the balance is between solubility and pH of the oral film for optimal drug absorption.

Suboxone is a sublingual film and disintegrates under the tongue in around five minutes.[15] Bunavail is adhered onto the buccal cheek and allowed to dissolve completely after application.[16] There were no scientific data disclosed pertaining to the dissolution time, but it has been suggested by users of Bunavail that it takes 15-30 minutes to dissolve.[21]

Absorption through mucosal membranes is a passive diffusion process and is concentration and time dependent. As the concentration of the API increases, the rate of flux across the membrane increases. If the flux is constant, more drug will be delivered across the membrane with a prolonged exposure as could be the case in Bunavail.

Thus, it is plausible that the much higher exposure of buprenorphine observed for Bunavail is a combination effect of both the higher pH environment, which brings along more unionised species for absorption, and longer duration for drug molecule to diffuse across the membrane. This helps explain why the lower dose of buprenorphine is required in Bunavail compared with Suboxone. This example illustrates the different approaches for drug delivery across the mucous membrane and is an embodiment of the understanding of the science in absorption.

Delivery of Macromolecules

To date, most of the applications of oral thin films have been in the delivery of small molecules. With the increasing number of large molecules being discovered and under development, there has been considerable interest in research to establish if transmucosal delivery is a viable route for administration.

Jin *et al* [12] studied the mucosal delivery of a potent peptide, Stichodactyla helianthus neurotoxin (ShK). They performed permeation studies using an *in vitro* Ussing chamber model and found no detectable level of florescent 5-Fam-ShK in the receptor cell after application onto untreated porcine buccal mucosa. When formulated with surfactant taurodeoxycholate hydrate or cetrimide, ShK in a chitosan muco-adhesive gel produced 0.005-0.13% and 1.1% respectively of the applied dose over a five-hour period in the receptor cell. Confocal microscopic examination of the mucosal fluorescence associated with 5-Fam-ShK showed enhanced buccal mucosal retention of the peptide. This demonstrated that the potent peptide could be transported across the buccal membrane when appropriately formulated.

There were also encouraging results from the 5-Fam-ShK chitosan-based (3%) gel formulated with or without cetrimide. When administered to mice it resulted in average plasma concentration of 2.6-16.2 nM at between 2-6 hours (Figure 5). These concentrations were substantially higher than the pM concentration required for therapeutic activity for the treatment of auto-immune disease. This suggests that the buccal route could be a suitable administration route for this potent peptide which otherwise needs to be administered parenterally.

Despite the promising results, the authors acknowledged the "higher" level of cetrimide used and that further work would be required to ascertain the appropriate level for incorporation to elicit its permeability-enhancing properties without unduly causing adverse irritancy.

Phillips *et al* [22] formulated an oral film containing insulin-gold ligand nanoparticles. They studied the bioavailability of insulin absorbed bucally from this film compared

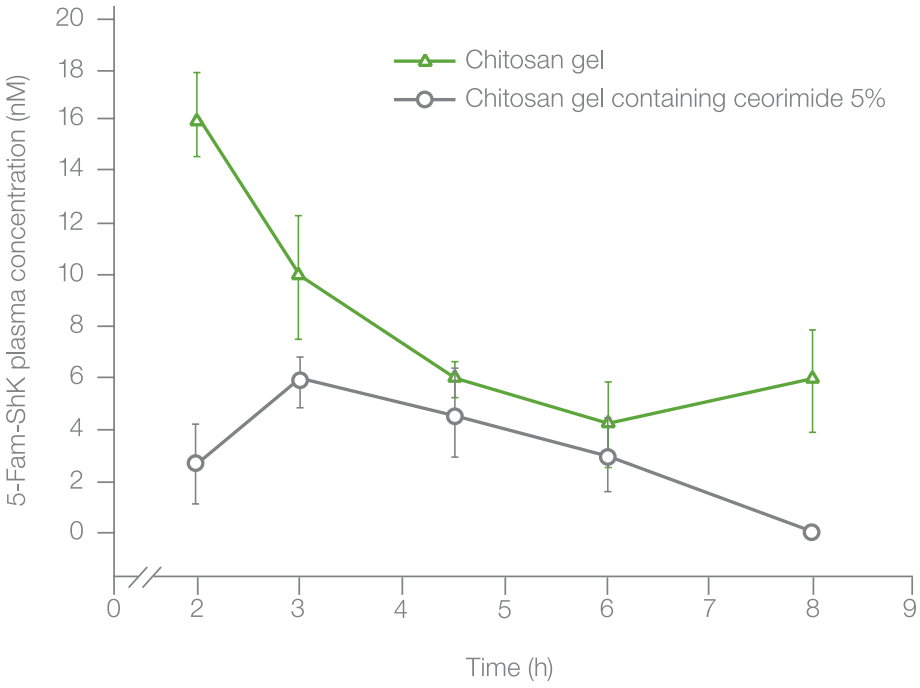


Figure 5: Plasma concentrations of 5-Fam-ShK in mice, following buccal administration of 5-Fam-ShK (10 mg/kg) in 4 mg of a 3% w/v chitosan gel with and without 5% w/w cetrimide. (Data presented a mean ± SEM (n=3-5).[12]

Treatment	Glucose consumed (g) Total	Total minus placebo	Per IU insulin administered
SC Insulin Aspart (n=6) Cohort 1 5 IU	135 ± 17	107 ± 21	21 ± 4 (0–600min)
TB Regular Insulin (n=6) Cohort 1 5 IU	87 ± 19	59 ± 23	12 ± 4 (0–600min)
Placebo (n=6)	28 ± 4 (endogenous) (0–600min)		

Table 2: Summary results from study of transbuccal film delivery of insulin.[22]

with subcutaneous insulin injection. They measured glucose infusion rates to estimate the pharmacodynamic effect and from there derived the bioavailability data. In their analysis, they suggested the ligand-insulin nanoparticle achieved 50% the pharmacodynamic effect compared with subcutaneous insulin. These encouraging results showed promise for the buccal delivery of larger molecules as a non-invasive approach.

CONCLUSIONS

This article has provided an overview of the fundamentals of transmucosal absorption, its mechanism and the science behind absorption. A thorough understanding of the physicochemical properties of the API, together with prudent choice of formulation excipients and system design, could lead to viable products with the desired clinical outcomes. Thin films offer significant advantages over peroral administration for drugs with high first-pass metabolism, especially in reducing drug exposure and side effects. Research into transmucosal delivery of large molecules and peptides also provides further optimism of the future of this novel dosage form.

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A NOVEL APPROACH TO THE ORAL DELIVERY OF BIOLOGICS, PEPTIDES AND ANTIBODIES

Mir Imran, from Rani Therapeutics™, provides an exclusive update on his company's groundbreaking robotic Auto-Pill™, which delivers a pain-free intestinal injection using a dissolvable needle made from materials that can be absorbed or easily passed out of the body. This approach allows the delivery of biologics of any molecular weight.

Over the past several decades, biologic therapeutics have proven to be highly effective treatments for a number of chronic diseases such as arthritis, diabetes, multiple sclerosis, plaque psoriasis, Crohn's disease and ulcerative colitis, among others. Collectively, these agents represent a market with annual sales exceeding US$200 billion (£150 billion), and sales growth in this area has steadily increased. In fact, between 2009 and 2012, the industry saw a 33% increase, with therapeutic proteins and monoclonal antibodies showing the greatest upwards trend.

> "With as many as 150 failed attempts over the past 40 years, oral delivery of biologics remains the "holy grail" of drug delivery."

Despite their blockbuster success, the delivery of biologics is far from ideal as the majority of these drugs can only be delivered by injection. As a result, patients must endure painful and frequent injections, some as often as daily, which can have a dramatic impact on a patient's quality of life and compliance.

There is no doubt that the oral delivery of biologics, peptides and antibodies would be a breakthrough for patients and a bonanza for pharmaceutical companies. With as many as 150 failed attempts over the past 40 years, oral delivery of biologics remains the "holy grail" of drug delivery. Most notably, oral delivery of insulin, as well as other peptides like somatostatin and PTH, have been attempted multiple times, with low-single-digit bioavailability, which makes them clinically and commercially impractical. These prior attempts failed primarily because pharmaceutical approaches designed to protect the proteins from degradation and digestion in the GI tract were unsuccessful.

When we founded Rani Therapeutics in 2012, we decided to take a completely new approach to the problem of oral delivery of biologics. The result is the Rani Auto-Pill™ – a robotic pill that delivers an intestinal injection without exposing the drug to the digestive enzymes. The patient takes what appears as an ordinary capsule, but the Rani Auto-Pill™ is a sophisticated device which incorporates a number of innovations, enabling it to navigate through the stomach and enter the small intestine where it goes through a transformation and positions itself to inject the drug into the intestinal wall.

HISTORY OF THE RANI AUTO-PILL™

We started with the premise that injecting the drug into the intestinal wall would be ideal because there are no sharp-pain receptors in the intestine, rendering the injection painless. In addition, the intestinal wall is highly vascularised which means that the drug once delivered will be quickly absorbed. With deep experience in engineering and materials science, we designed the Rani Auto-Pill™ to ensure that the drug would stay protected within the pill until injected. To ensure safety of the Rani Auto-Pill™, we selected US FDA-approved injectable and ingestible materials that are either safely absorbed or easily passed out of the body (see Figure 1).

One decision we made early on was to formulate the biologic drug with appropriate excipients, in solid form. This has two distinct advantages; first, we can maximise the amount of drug in a small volume and second, the drug in solid dry form has longer shelf-life than in liquid form. The next question was what kind of needle to

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use for the injection? Metal needles were not an option for obvious reasons…no one wants to swallow metal needles! We decided to create tiny dissolvable needles which would contain the biologic drug. The idea was to deliver the dissolvable needle containing the solid drug into the intestinal wall. The drug would be released after the needle is injected and the needle is dissolved.

The next challenge was to figure out a way to develop enough force to deliver the needle into the intestinal wall. Initially, we considered levers and springs, but quickly ruled that out as no patient will want to swallow springs. We settled on the use of an inflatable balloon-like structure that would supply the force to deliver the needle. Balloon inflation happens when carbon dioxide is produced from a chemical reaction between citric acid and sodium bicarbonate that takes place inside the balloon, and this creates the pressure needed to inject the needle.

The balloon, including the needle and drug, are assembled in a cellulose capsule shell which is then coated with a pH-sensitive polymer that is designed to dissolve at a pH >6.5. This ensures that the capsule does not dissolve in the stomach where the pH is generally <5. Once the capsule goes past the duodenum, and the pH rises above 6.5, the outer shell dissolves, triggering the chemical reaction inside the balloon. The balloon then inflates and delivers the needle with the drug. Once the needle is delivered, all that is left is a deflated polymer, having the consistency of a bell pepper skin or tomato skin, which the patient passes out.

We believe this approach will allow us to deliver biologics of any molecular weight regardless of its structure or properties. So not only small peptides and proteins but even therapeutic antibodies, and RNAi therapies can easily be delivered by Rani's technology. The Rani route of administration presents additional advantages for certain biologics, such as those targeting the liver. Unlike subcutaneous delivery, where the drug first targets the systemic circulation and ultimately makes its way to the liver, with our approach the first organ the drug goes into is the liver. Thus, Rani Auto-Pill™ could potentially be very useful for drugs such as PCSK9 antibodies and insulin which target the liver.

The one limitation of the Rani Auto-Pill™ is how much drug can be put inside the needle. Currently, the limit is about 3-5 mg per capsule that should allow for the delivery of ~70-80% of all biologics (therapeutic peptides, proteins and antibodies). Drugs that are given in high doses, such as hundreds of milligrams at one time, may not be suitable for the Rani platform. However, the small payload is not a limitation for most peptides, proteins and therapeutic antibodies.

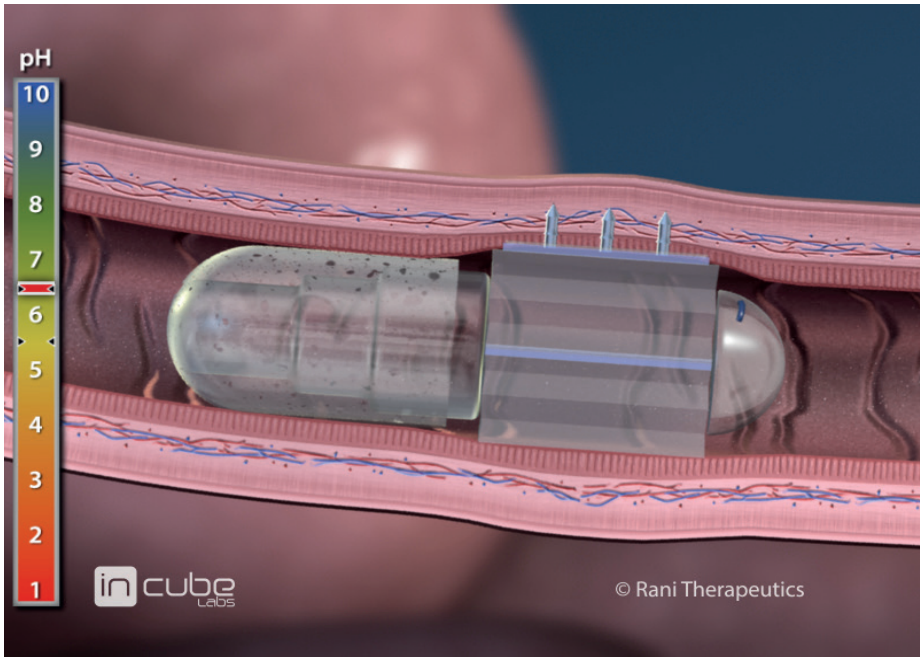

Figure 1: A diagrammatic depiction of the Rani Auto-Pill™. The current Auto-Pill is a 000 size, or the equivalent of a calcium or fish oil pill, and currently includes one needle for drug delivery. Over time, we envision multiple needles will be possible to increase payload.

RANI'S PATH FORWARD

This is a very exciting time for our company. We have brought together a diverse group of experts across disciplines including biology, material science, engineering, pharmacology and manufacturing. We are currently conducting a variety of studies in relevant pre-clinical models. The goal is to achieve safe and reliable delivery of the needles. Initial studies have shown that the Rani route of administration is as effective as subcutaneous injections. We have a strong patent position with more than 25 approved patents and 50 pending applications. We are now collaborating with two large pharma companies – Novartis and AstraZeneca – to test different molecules on the Rani platform.

CONCLUSION

We recognise that we are working on one of the biggest challenges in drug delivery, something we do not take lightly. We know there are many challenges ahead of us, but we stay focused on our mission. Rani has the potential to transform how biologics are delivered and most importantly, the potential to radically improve the quality of life for millions of patients suffering from chronic diseases.

ABOUT RANI THERAPEUTICS

Rani Therapeutics was developed at InCube Labs, a multi-disciplinary life sciences R&D lab focused on developing breakthrough medical innovations. The company has raised more than $70 million. Investors include Novartis, AstraZeneca, Google Ventures, Buttonwood, GF Ventures, KPC Pharmaceuticals, Virtus Inspire Ventures, Ping An Ventures, InCube Ventures and VentureHealth.

ABOUT THE AUTHOR

Mir Imran is a prolific medical inventor, entrepreneur and investor, who has founded more than 20 life sciences companies and holds more than 400 issued and pending US patents. Many of Imran's innovations have resulted in new standards of care, including the first FDA-approved Automatic Implantable Cardioverter Defibrillator. For more information, please visit: www.ranitherapeutics.com and www.incubelabs.com.

THE EMERGENCE OF CONTROLLED-RELEASE POWDERS FOR ORAL ADMINISTRATION

Though the number of approved controlled-release powder formats is modest, a rising number of pharmaceutical companies and manufacturing organisations are incorporating controlled-release powder manufacturing to their portfolios to address the growing dosage form problem for paediatric and geriatric patients. Cory Berkland, PhD, and Nathan Dormer, PhD, from Orbis Biosciences look at what this delivery system can offer.

The importance of providing safe and efficacious formularies for populations with dysphagia, such as paediatric and geriatric patients, has been continually cited as an area in need of improvement for pharmaceutical companies and the providers who administer their products.[1-16]

The relative paucity of dispersible format oral products means clinicians and compounding pharmacies have to use alternative solutions to treat their patients that are not always backed by supporting safety, bioavailability and stability studies. Tablets are sometimes administered with improvisatory methods such as crushing the dosage form and mixing with food or drink. These methods not only lead to dosing errors and decreased efficacy, but can perpetuate non-adherence if the active pharmaceutical ingredients (API) are foul-tasting.[17-20]

Due to these issues, The Institute for Safe Medical Practices (ISMP) regularly updates a "Do Not Crush" list, which lists several hundred dosage forms that cannot be compounded due to special controlled-release properties, taste-masking or API protection.[1-6,10-13] The dosage form problem affects over half of the global population (under 18 and over 65 years of age).[17-20] Dosing protocols for populations with dysphagia or resistance to taking traditional capsules or tablets fail to address many formulation design criteria.[21, 22]

MASKING TASTE ISSUES

A number of APIs taste extremely bitter and some granule and tablet-coating techniques can result in an unpleasant feel in the mouth due to irregular surface finishes. It has been estimated that 50% of patients with organoleptic sensitivities are reluctant to take their medicine, with the majority of those reporting poor taste as a large contributor to non-compliance.[12]

> "Recent advances have enabled extended release and taste-masking of orally administered APIs, but the breadth of application currently covers less than 1% of marketed drugs."

Artificial flavours alone are often unable to overcome the extremely unpleasant taste of many active ingredients in syrups and suspensions.[1,10,11] Moreover, efforts to mask flavours using coatings or microencapsulation often result in poorly-controlled, polydisperse particle diameters that result in a sand-like consistency. Ideally, a dosage form would consist of taste-masking with negligible texture while maintaining other extended- or delayed-release properties. The age, weight, surface area and metabolic proclivities of patients may also require substantial dosing considerations that are not linearly scaled.[13]

TABLET SIZE ISSUES

Achieving controlled-release kinetics with tablets is a relatively simple process, as the size and form factor of the dosage form

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lends to using robust coating methods, sometimes with several layers.[17,20] Capsules have the advantage of being injection moulded, extruded or die pressed with gelatines and other controlled-release polymers in a repeatable, high-throughput manner, enabling large doses of medication in a modest form factor. Tablets are simply pressed, then coated with subsequent layers of controlled-release components, which makes translation of specialised controlled release (e.g. delayed or extended) simple.[17,20]

CONTROLLED-RELEASE POWDER FORMATS

Due to the large format of controlled-release pills and capsules, the foul taste of traditional syrups and suspensions, and the lack of controlled-release options for APIs tableted and encapsulated in nearly 85% of marketed drugs,[25,26] many pharmaceutical and contract manufacturing organisations (CMOs) are focusing research and development efforts on controlled-release powder formats, which combine the stability of solid oral dosage forms and dose titration advantages of liquids. These alternatives to tablets address many of the deficiencies discussed earlier, but can still be fraught with inadequacies such as multiple-step manufacturing and inconsistent particle sizes.

> "Micro- and nanoparticulate powders are manufactured with myriad processes, but the primary motivation is integration of controlled-release mechanisms to govern particle disintegration and API dissolution."

The size of such dosage forms, however, renders pills and capsules impractical for patients with swallowing difficulties. Data from current products indicates that the average size of a controlled-release pill is nearly 1.5 cm in length.[23] Physiological studies demonstrate that swallowing becomes difficult when the dimension of the object being ingested is greater than half of the oesophageal diameter, which is 2.0 cm for the prototypical adult.[24] Moreover, the average extended or delayed-release pill may be too large to be swallowed easily.

The merits of tablets are that they contain the volumetric space to:

- Deliver a large payload of API
- Use special controlled-release mechanisms
- Circumvent shelf stability challenges.

Where large tablets and capsules present swallowing and administration challenges, liquid formats succeed in dose titration most of the time. The advantages beyond ease of dosing are limited in traditional syrups, however. Liquid formats are usually not extended-release, have little-to-no taste-masking and can contain API particles prone to settling and aggregation if not reconstituted properly prior to administration, which have resulted in risks to patient safety.[10,12-16] Recent advances have enabled extended release and taste-masking of orally-administered APIs, but the breadth of application currently covers less than 1% of marketed drugs.

Micro- and nanoparticulate powders are manufactured with myriad processes, but the primary motivation is integration of controlled-release mechanisms to govern particle disintegration and API dissolution.

The requirement of achieving controlled release universally relies on physical sequestration of the API via one or more physicochemical mechanisms, which typically requires multiple steps.

A powder form factor, however, can present unique challenges to achieving controlled release coatings due to:

- The high surface area of particles
- Irregular sizes of particles within the powder
- The number of process steps required to ensure predictable performance and reasonable quality of the final product.

Taste-masking can still be achieved with powders, however, when a coating or other chemical modification is applied.[14,25,26]

Precursor particle method

The most straightforward method for achieving taste-masking and controlled release with powders employs a two-step process in which a precursor particle is manufactured by various means, then coated with one or more layers containing controlled-release materials. Precursor particles can either be:

- Milled API crystals
- API co-mixed with inert bases or controlled-release excipients
- A 100% inert core sans API.

Figure 1: Next-generation powder manufacturing technologies (left) can provide narrow particle size distributions while offering taste-masking and controlled release in a single step, which overcomes limitations provided by traditional powder manufacturing methods (right).

These precursors can be manufactured by any method, which include traditional vibratory methods, congealing/spinning disk atomisation, prilling, hot-melt extrusion (HME) and spheronisation, aqueous dispersions, blending/bulking, electrohydrodynamic spraying (EHDS), or spray drying.[27-34] Material selection for the precursor particle relies on process capabilities, desired end-product controlled-release properties, API thermal and oxidative stability and desired physical properties (surface features, density, friability, hardness, etc).

If taste-masking, delayed-release or stability-enabling properties are required, the precursor particle advances to subsequent traditional layering steps using fluidised beds, Würster coaters, spray/pan coating, or coacervation.[16,35-38] Materials of choice for the secondary coating steps are selected for reasons commensurate with precursor particles (i.e. material compatibility, controlled-release behaviour and stability). The final dosage form, typically granules in the 200–500 µm diameter range, can then be re-suspended, packaged in sachets or sprinkle capsules, placed in dissolving tongue strips, co-lyophilised with other materials for orally-disintegrating tablets (ODTs), or reconstituted in syrup.

Chemical modificiation

The history of manufacturing controlled-release powders by adding one or more coating steps to API-rich cores is very established. These techniques are, however, divergent from state-of-the art techniques that focus on chemical modification of the API and/or substrate using ion exchange resins.[39-41] The main advantages that these methods can yield are liquid stability and deterring abuse of scheduled APIs, such as opiates and amphetamines.

While revolutionary, drug complexation employs a number of manufacturing steps that far surpasses that of simple bead layering, and still usually includes a final coating step.[16,35-38] Indeed, developing controlled-release powders has traditionally employed combinations of manufacturing mechanisms and complex chemistry, which achieve substantial advantages over traditional pill and capsule formats, enabling extended- and delayed-release liquid suspensions and powders, while providing taste-masking as-is, in a liquid constituent, or further compounded.

Precision Particle Fabrication™ technology

The major criticisms of these methods, however, focus on the number of process steps and excipients. Thus, it comes as no surprise that manufacturers are investigating less complex chemistry and single-step manufacturing methods for producing controlled-release powders (Figure 1). One such technology platform, Precision Particle Fabrication™ technology, is a manufacturing scheme that creates oral controlled-release microsphere and microcapsule powders as low as 75 µm in a single step, without the need for secondary coating steps or sieving to remove particles that are too large or too small.[42-47]

CONCLUSION

Though oral dosage forms such as pills and tablets are sufficient for many individuals, a significant fraction of the world's population suffers from swallowing problems, taste sensitivities or an avoidance to taking medication of any format. As these patients are afflicted with acute or chronic illnesses, sometimes a lack of format flexibility and dosage options limits treatment. An emergence in controlled-release powder manufacturing has taken place over the last decade, replacing large tablets with dispersible and dose-flexible alternatives.

The methods for making controlled release powders vary, but typically include forming an API/excipient core precursor then coating with one or more controlled-release layers for a finished product. Contemporary techniques incorporate chemical modification and sequestration of the API, prior to secondary coating steps. Next-generation techniques eliminate the need for multiple steps, achieving even coatings while maintaining monodisperse size distributions and high API content at small overall particle size to enhance palatability.

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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.

> "With more products emerging in development pipelines and regulatory approvals, the potential for mucosal thin film delivery is finally gaining recognition."

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.

> "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."

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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Scott Barnhart is the Technical Director for ARx, LLC, a wholly owned subsidiary of Adhesives Research Inc. With more than 20 years of R&D experience, Scott's career has focused on drug matrix formulation and process capabilities for transdermal drug delivery systems and in the development of the company's dissolvable thin film drug delivery systems. Scott earned his BSc in Chemistry and Biology from The Pennsylvania State University and his MSc in organic Chemistry from Shippensburg University.

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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METHODOLOGIES FOR DEVELOPING s-SEDDS

The use of solid self-emulsifying drug delivery systems is growing in popularity as they offer advantages over liquids, such as the ease with which they can be incorporated into tablets and other solid oral dosage forms, their stability and ease of manufacture. John K Tillotson, RPh, PhD, looks at the various methods available for manufacturing these systems and explores the possibilities of optimising these methods in the future.

Lipid-based drug delivery (LBDD) is an effective method of improving the solubility of BCS Class II and Class IV compounds and the permeability of certain BCS Class III and Class IV compounds. Typically, LBDD systems are formulated by dissolving the therapeutic compound in one or more lipids to form a pre-concentrate. Subsequently, this pre-concentrate forms a drug containing oil-in-water emulsion in the gastrointestinal (GI) tract through the actions of enzymes and bile salts or by self-emulsification of the lipid components.

> "The formulation of solid LBDD pre-concentrates is not a trivial process as attention needs to be paid to the physical state of both the therapeutic compound and the pre-concentrate lipids."

Traditionally, the employed lipids have been liquid at room temperature. Recently, it has become of greater interest to develop solid LBDD pre-concentrates which can offer certain advantages over liquids, most specifically ease of incorporation into tablets and other solid oral dosage forms, improved stability, and specific dosage form characteristics such as sustained-release or abuse-deterrence. The formulation of solid LBDD pre-concentrates is not a trivial process as attention needs to be paid to the physical state of both the therapeutic compound and the pre-concentrate lipids, as well as the dispersion of the solid pre-concentrate into an oil-in-water emulsion in the GI tract, in order to ensure drug delivery.

METHODS OF MANUFACTURING S-SEDDS

There are many methods available for the preparation of solid self-emulsifying drug delivery systems (s-SEDDS) including filling capsules with semi-solids, adsorption of the SEDDS pre-concentrate onto suitable substrates, congealing and nanoparticle formation.[1]

Semi-Solid Capsule Filling

In this method of s-SEDDS manufacturing, there is a combination of SEDDS pre-concentrate components, which are liquid at room temperature with a solidifying agent, which is normally a lipid surfactant or co-surfactant that is solid at room temperature.

The components are brought together in the liquid state and filled into capsules and

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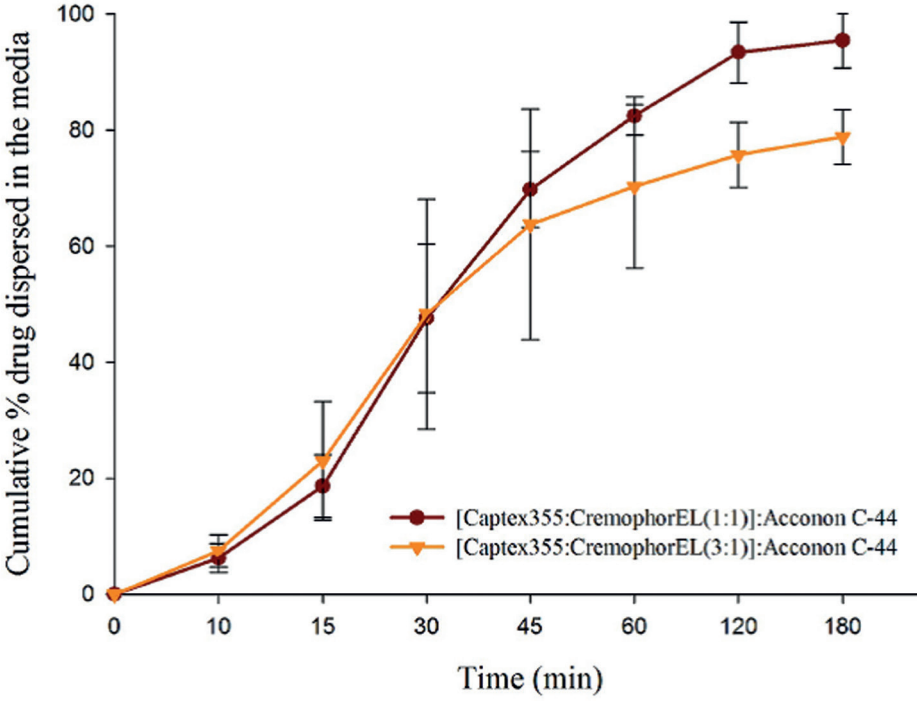

Figure 1: Dissolution of probucol from s-SEDDS.

allowed to solidify. A typical approach is to bring together the liquid pre-concentrate components with the solidifying agent under heat in order to create a continuous liquid phase of all materials.

The active pharmaceutical ingredient (API) is then dissolved in the hot pre-concentrate, and subsequently, the hot pre-concentrate is then filled into capsules. As the hot pre-concentrate cools, the solidifying agent comes out of its molten state and incorporates the liquid pre-concentrate components into a solid form or semi-solid form, which contains the active.

Selection of the proportion and type of pre-concentrate components is very important for two reasons:

- The components must be selected in a manner allowing for re-solidification of the pre-concentrate upon cooling
- Solid / semi-solid pre-concentrate should disperse into, preferably, a micro-emulsion upon contact with aqueous media.

For example, it was found that for a probucol formulation a combination of a solid lauroyl macrogolglyceride, medium chain triglyceride and an ethoxylated castor oil were suitable for solidification, dissolution and emulsifying characteristics (see Figure 1).[2]

In the same study, propylene glycol monocaprylate and glycerol monocaprylocaprate could not be suitably solidified by the lauroyl macrogolglyceride. Additionally, the addition of an ethoxylated castor oil as a co-surfactant was necessary to provide for adequate active dissolution and emulsion formation in the aqueous environment.

Substrate Adsorption

The objective of this method of manufacturing is to deposit a liquid SEDDS pre-concentrate onto a suitable carrier in order to produce a free-flowing, SEDDS-containing powder, which can be employed for subsequent unit operations such as tableting. These SEDDS powder systems may be prepared by various methods including direct mixing, high-shear granulation, vacuum deposition and fluid-bed layering/granulation.

As with any SEDDS system, it is important to optimise the pre-concentrate components, such as primary and secondary solubilisers, surfactants and co-surfactants to achieve maximum drug loading in the pre-concentrate as well as suitable emulsion characteristics such as emulsion globule size. Once an optimal SEDDS pre-concentrate is developed, it can be applied to a substrate as described above.

Election of the substrate is also important, as well as the interaction of the substrate with the pre-concentrate. The most important characteristics of the substrate are:

- The extent to which the liquid pre-concentrate can be absorbed by the substrate

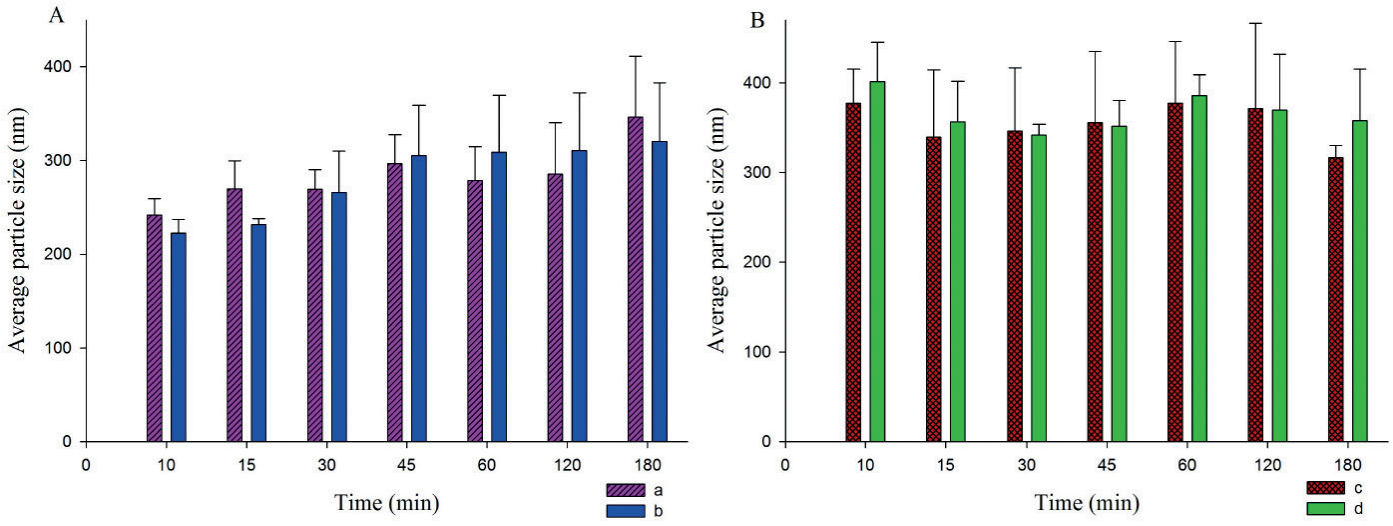

Figure 2: Average emulsion globule size for (A) 1:1 Captex 355 EP/NF:Cremophor EL, and (B) 3:1 Captex 355 EP/NF:Cremophor EL [(a) without probucol, (b) with probucol, (c) without probucol, (d) with probucol.][2]

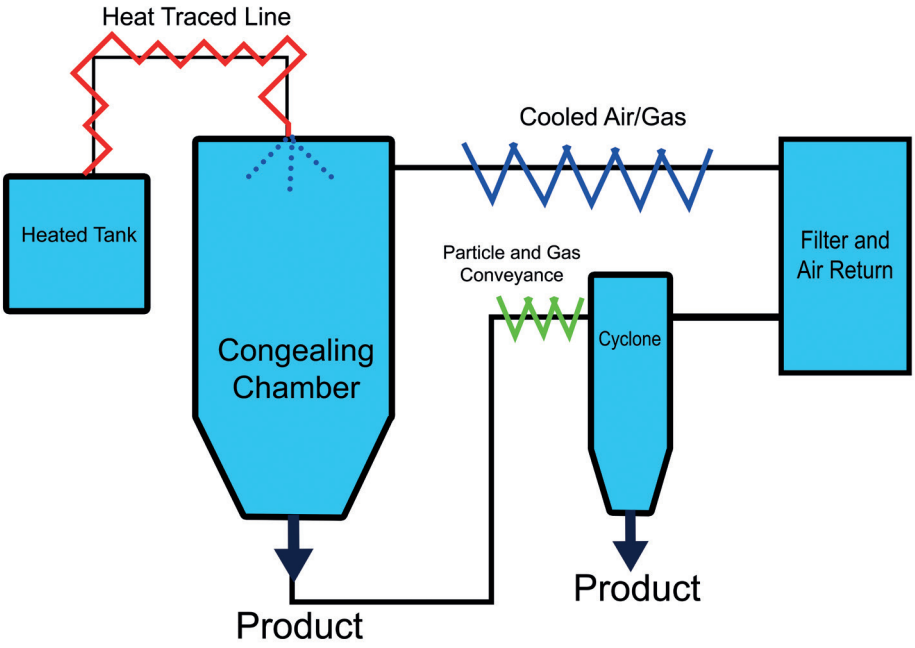

Figure 3: Schematic of a spray-congealing system.

- The ease with which the pre-concentrate is released by the substrate
- The ability of the substrate to maintain flow characteristics after SEDDS deposition
- The ability of the substrate to maintain compaction characteristics after SEDDS deposition, especially for tableted dosage forms.

Multiple SEDDS pre-concentrate formulations containing rosuvastatin were deposited onto colloidal silicon dioxide by mixing, followed by dissolution tests.

Of 12 s-SEDDS formulations tested only one provided adequate drug loading, particle size and acceptable drug release.[3] This highlights one of the primary difficulties with this manufacturing methodology – obtaining adequate drug release from the s-SEDDS. As in the aforementioned study, silica substrates are often chosen for this application, as they can absorb large amounts of oil. However, due to the hydrophobicity and small pore size of the silica, the pre-concentrate is not always readily released from the carrier. This results in incomplete drug release.

Additionally, it is possible to adsorb lipid pre-concentrates onto the surface of water soluble substrates, such as mannitol or lactose; however, this may result in a tacky, non-free-flowing powder. For this reason, the deposition of SEDDS pre-concentrate onto water soluble substrates may only be suitable for low-dose actives, requiring less pre-concentrate for dissolution of the active, leading to a lower pre-concentrate proportion in the s-SEDDS.

Spray-Congealing

In spray-congealing, a molten lipid system carrying an active is sprayed into an expansion chamber where the molten material re-solidifies at the lower temperature to produce an active carrying multi-particulate s-SEDDS (Figure 3). Essentially, the molten lipid matrix is the pre-concentrate for s-SEDDS prepared in this manner.

The particle size distribution of the multi-particulate is determined by nozzle diameter and air pressure brought into the nozzle during spraying. Alternatively, in certain systems, a rotary disc which receives the molten material from a nozzle can control the particle size of the multi-particulates by controlling the rotational velocity of the disc.[4]

The objective of an s-SEDDS prepared by congealing is to maintain the active in the amorphous state (if possible) during and after processing. For this reason, it is preferable to match the melting point of the active with the melting point of lipid pre-concentrate components.

In practice, this is not always possible, as the lipids tend to have lower melting points than many actives. This does not preclude employing spray-congealing as a unit operation for improving the solubility of actives. In fact, in an s-SEDDS for glibenclamide prepared by spray-congealing, despite the presences of crystalline glibenclamide in the final s-SEDDS multi-particulate, a five-fold increase in the dissolution rate of glibenclamide was obtained from the s-SEDDS as compared with the raw active.[5]

This indicates that spray-congealing can provide significant increases in dissolution rate even when some of the active remains in the crystal state after processing. Additionally, as the components of the molten pre-concentrate are solubilising lipids, the active can dissolve into the molten lipid matrix rather than melt entirely. The development of a pre-concentrate blend for s-SEDDS for spray-congealing, similar to the development of a liquid SEDDS pre-concentrate, requires formulation optimisation towards maximising drug solubility and achieving the desired emulsion characteristics.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) s-SEDDS are very small multi-particulate systems typically with a size of 100–200 nm. There are several manufacturing methods for producing SLN s-SEDDS, including high-shear homogenisation, high-pressure homogenisation (HPH) and solvent emulsification/evaporation.[6]

The most common of these is HPH, wherein a lipid matrix (containing API) is pushed through a very narrow gap (several microns) under high pressure (100-2000 bar) to create nanoparticles from the resulting high shear forces generated in this process. In hot HPH (Figure 4, left-hand side), the homogenisation is carried out at temperatures above the melting-point of the lipid pre-concentrate; and therefore, it is the homogenisation of an emulsion. In cold HPH (Figure 4, right-hand side), the conditions are controlled (refrigeration) such that the heat generated by the process is well below the melt point of the excipients present. It is noted that for both hot and cold HPH, the active must first be incorporated into the molten pre-concentrate lipids. One major advantage of cold HPH is that it can be employed to process heat labile actives.

s-SEDDS SLNs can be administered by multiple routes including peroral, transdermal, parenteral, intraocular, inhalation and transfollicular.

There are three basic models proposed for the incorporation of actives into manufactured s-SEDDS SLNs:

- Homogeneous matrix
- Active-enriched shell
- Active-enriched core.[7]

The structure ultimately obtained is a function of the active and the pre-concentrate lipids, as well as the manufacturing unit operation. The type of API distribution in the lipid can have a profound effect on release characteristics, as an active-enriched shell will likely release more rapidly; while in contrast, an active-enriched core may lead to diffusion-based sustained release.

Ultimately, the formulation of s-SEDDS SLNs is optimised on the same basis as other s-SEDDS formulations by optimising API solubility and loading with the desired characteristics of the final emulsion.

CONCLUSION

While liquid SEDDS systems have been more commonly employed in the pharmaceutical industry, there are many advantages to s-SEDDS formulations. These include improved stability, ease of manufacture and the ability to formulate modified release characteristics.

While there are many techniques to manufacture s-SEDDS resulting in products with varying functionalities and applications, the optimisation of the pre-concentrate lipid components is the same as for liquid SEDDS: optimisation is based upon maximising drug solubility and loading as well as the final emulsion characteristics of the pre-concentrate.

While the concept of s-SEDDS has been around for quite some time, further research and optimisation of these formulations must be realised, in order for this dosage form to be more readily accepted and employed in marketed pharmaceutical products.

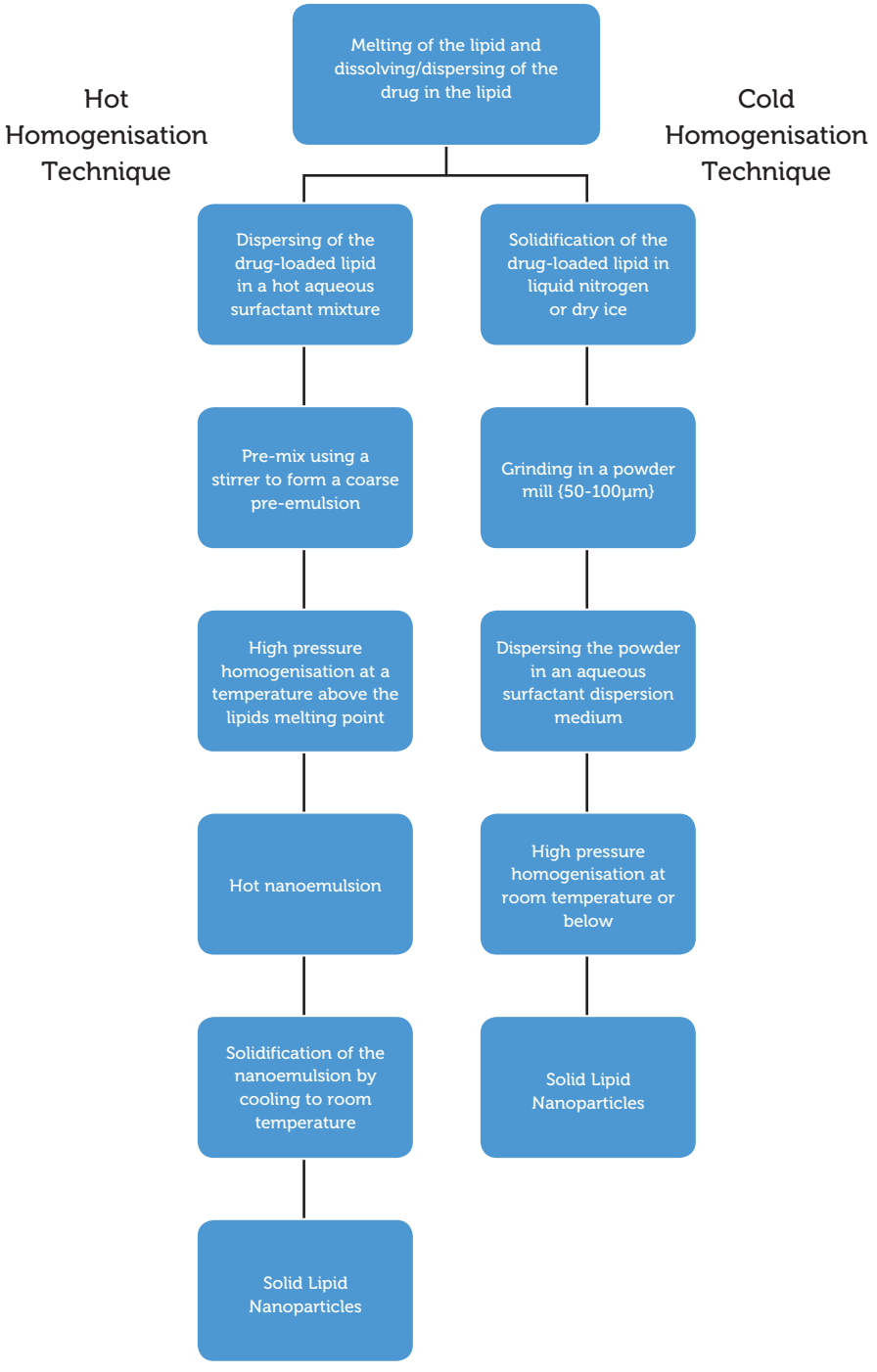

Figure 4: Schematic of SLN production by hot and cold HPH.[6]

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ABOUT THE AUTHOR

John Tillotson's research areas include functional lipids, SEDDS system development and direct compression tableting.

NOVEL ORAL DRUG DELIVERY: INNOVATING TO SIMPLIFY

In this article, Rashmi Nair, M Pharm, Senior Scientist, Formulation R&D, and Praveen Raheja, M Pharm, Principal Scientist, Formulation R&D, both of Dr. Reddy's Laboratories, Custom Pharmaceutical Services division, use case studies to illustrate their company's approach to simplifying existing oral drug delivery systems, including osmotic and matrix tablet technologies.

Drug delivery is a very important aspect for consideration during any drug development. The clinical and commercial success of a drug can be greatly affected by the route of administration as well as the drug delivery formulation. Given the advantages of oral drug delivery,[1] it has been an area of progressive evolution.[2,3]

The necessity to improve a drug's functional aspects like dosage regimen, *in vivo* drug stability, bioavailability, etc, has been the key driver of innovation in oral drug delivery. Some of these innovations brought complexity of product design and the manufacturing process. Various proprietary technologies have become the costly sophisticated solutions for oral drug delivery. Without undermining the importance of these drug delivery technologies, it is imperative to understand what creates a successful drug delivery system and evaluate whether existing drug delivery technologies can be simplified to suit conventional manufacturing. The following case studies for oral, controlled drug delivery of small molecules show that systematic science can simplify some of the sophisticated technologies.

APPROACH FOR SIMPLIFICATION

Defining the objective of product development with detailed enlisting of target product features is the first step. This should be followed by identifying what aspect of product or process requires simplification and possible alternatives that could be evaluated. Experimental design for testing the proposed alternative approach is the final stage. A typical step-plan for product development is depicted in Figure 1. Customised schemes of development are provided here with respective case studies.

CASE STUDY 1: OSMOTIC TABLETS SIMPLIFIED

The Osmotic Release Oral System (OROS) developed by ALZA Corporation (now J&J) in the 1990s is a commercially successful technology with various products incorporating it available in the market.[4] Merits of this technology have been validated with various drugs and therefore, for a formulator, it is probably the first choice when it comes to developing zero-order drug release for any product.

> "Various proprietary technologies have become the costly sophisticated solutions for oral drug delivery. Without undermining the importance of these drug delivery technologies, it is imperative to understand what creates a successful drug delivery system and evaluate whether existing drug delivery technologies can be simplified to suit conventional manufacturing."

Small laser drilled holes on the tablet surface provide precise drug release. However, there are limitations like the complexity of manufacturing requiring a different machine, a non-deformable tablet that remains as end product, and the technology associated cost. A development scheme for this case is depicted in Figure 2. Pseudoephedrine hydrochloride tablets 240 mg utilising OROS

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technology were taken as the target product. With immediate-release and extended-release components, it was a challenge to obtain zero-order drug release. Nevertheless, a matrix tablet was developed that was coated with extended-release coating and further coated with a drug layer. A successful bioequivalence study proved the validity of this work. Figure 3 depicts the approach summary.

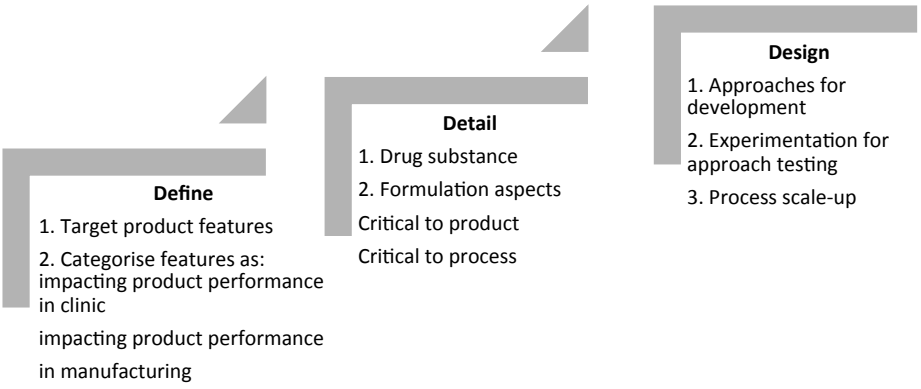


Figure 1: A typical step-plan for systematic product development.

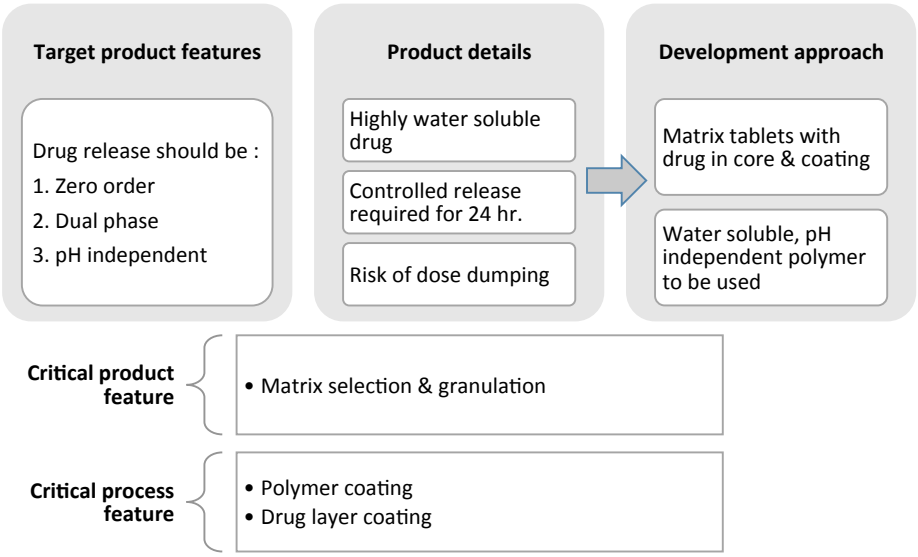


Figure 2: Scheme for development of matrix tablets.

CASE STUDY 2: MATRIX TABLETS MINIATURISED

A high-dose, highly water soluble drug required a compact dosage form. The marketed product was a large capsule with extended release pellets. This product was difficult to swallow and was not accepted well by patients. Mini matrix tablets were developed which resulted in product and process improvement. A mixture of high viscosity HPMC and carboxy methylcellulose salt were used in the matrix. The pelleting process took about 18 hours per batch manufacturing, whereas this approach simplified the process and reduced process time to less than six hours per batch. Humidity control was a critical consideration for extended-release coating of pellets. With this approach ambient conditions could be used and all process happened on conventional machines. The development scheme and approach summary are presented in Figures 4 and 5, respectively.

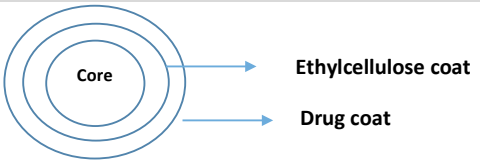
CASE STUDY 3: FLEXIBILITY BY DESIGN

A clinical study program for an NCE was conducted with a tablet dosage form. The study program required multiple, dose-ranging studies for monotherapy and additionally a fixed-dose combination.

Product design

75% drug in core

25% drug in drug coat



Performance testing (in-vitro)

Time (hr.)	% Drug release in dissolution study	
	SUDAFED 24	CPS product
1	27	27
2	29	28
6	47	48
12	76	78
18	96	94
24	103	99

Performance testing (in-vivo)

Mean linear plot for fed state bioequivalence study

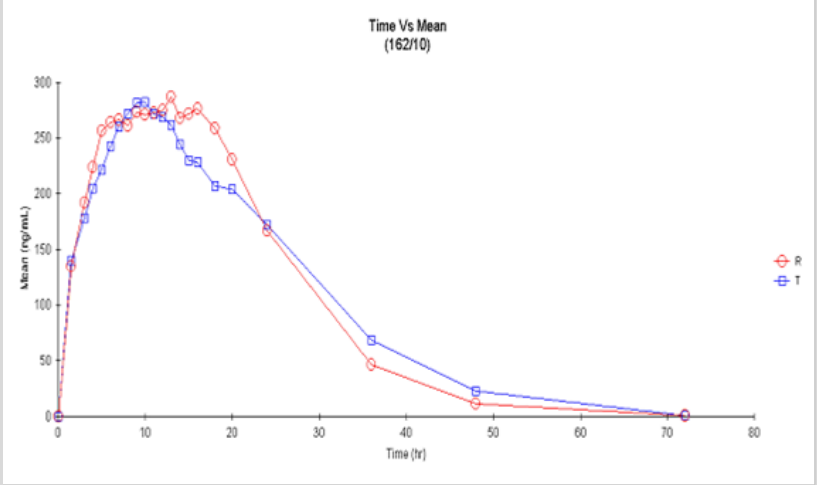


Figure 3: Summary of concept-to-product for matrix tablets.

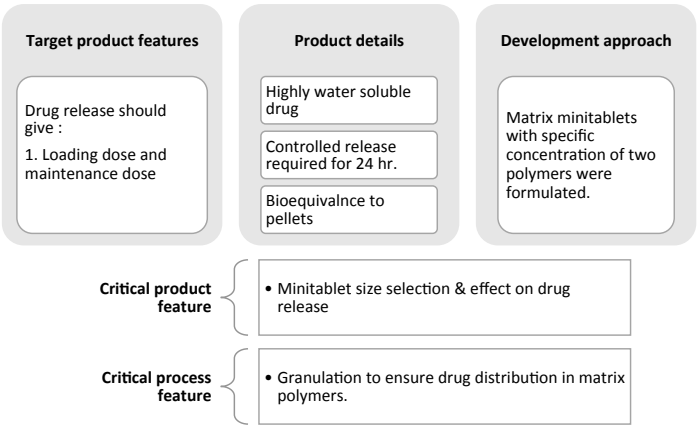
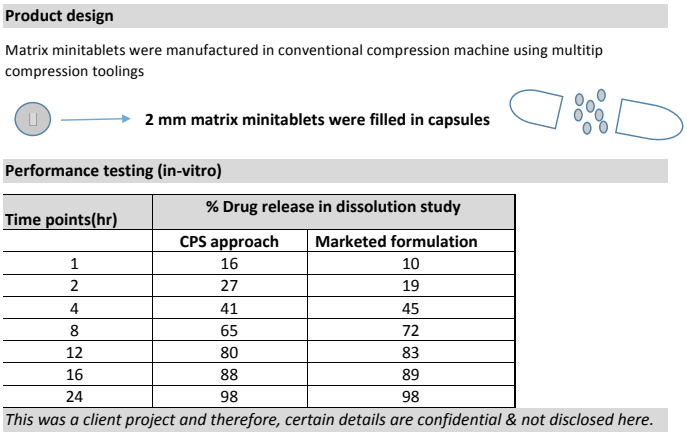


Figure 4: Scheme for development of matrix minitablets.



Time points(hr)	% Drug release in dissolution study	
	CPS approach	Marketed formulation
1	16	10
2	27	19
4	41	45
8	65	72
12	80	83
16	88	89
24	98	98

This was a client project and therefore, certain details are confidential & not disclosed here.

Figure 5: Summary of concept-to-product for matrix minitablets.

Different drug release profiles were required. A Wurster process for pellets was developed which allowed production of multiple drug release profiles from a single batch. This provided flexibility of adjusting the dose (by changing fill weights of pellets), tailoring different drug release profiles (by changing coating load) and making different permutations and combinations with the second drug for the fixed dose combination product.

CONCLUSION

In each of the above cases, the objective of the product development team was to design the best possible product utilising simple scientific principles and product experience. A thorough understanding of various aspects of a drug product, like the physicochemical properties, pharmacokinetics, target sites of absorption and action, excipients, manufacturing processes and critical product parameters, are essential to assess the development approach for a drug product holistically.

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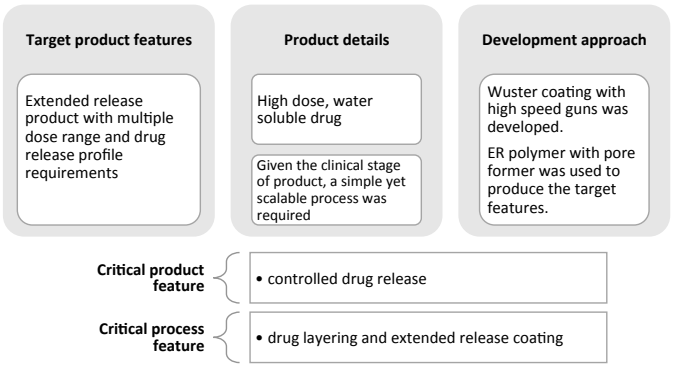
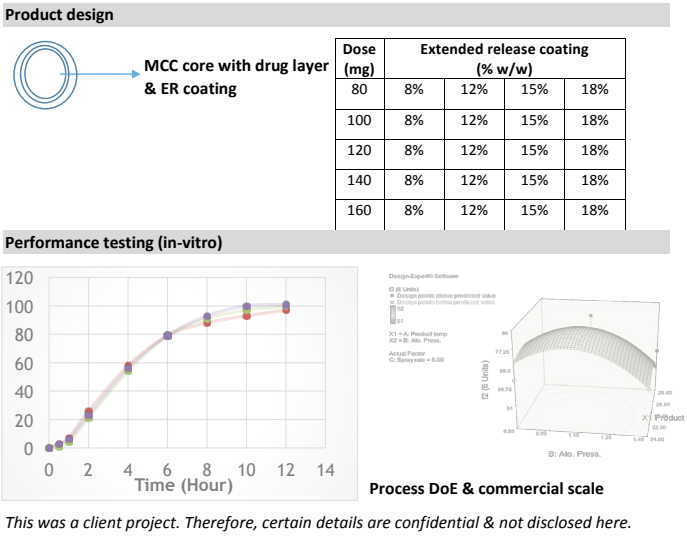


Figure 6: Scheme for development of extended release pellets.



Dose (mg)	Extended release coating (% w/w)			
80	8%	12%	15%	18%
100	8%	12%	15%	18%
120	8%	12%	15%	18%
140	8%	12%	15%	18%
160	8%	12%	15%	18%

This was a client project. Therefore, certain details are confidential & not disclosed here.

Figure 7: Summary of concept-to-product for extended release pellets.

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WHY ORAL DISINTEGRATING TABLETS?

In this piece, Carmen Popescu, PhD, Senior Project Coordinator, Roquette, provides an overview of the Orally Disintegrating Tablet (ODT) landscape, describing how these dosage forms can be used to improve and differentiate drug products, different manufacturing methods and how this class of oral delivery system might be applied in the future.

Oral Disintigrating Tablets (ODTs) are patient-centric drug delivery systems (for example, for paediatrics, geriatrics, and psychiatric patients with dysphagia) designed to increase patient compliance. ODTs are preferred to classic dosage forms (swallowable / chewable / suckable tablets) due to ease of administration (portability, "on the go") without water, pleasant taste and mouth-feel – more of "a treat" than a treatment. Reduced first-pass metabolism, faster onset of action, better absorption and, in turn, improved bioavailability are their very appealing benefits. Manufacturers' attraction for these dosage forms resides in improved lifecycle management, market differentiation, innovation and brand creation. Moreover, in recent years, we can see their remarkable expansion from Rx to OTC, nutraceuticals (vitamins, minerals, etc) and biologics. In response to the increased popularity of ODTs on the market, the excipients industry created ready-to-use platforms in order to ease the formulation process.

> "Recently, the US FDA approved SPRITAM (levetiracetem) ODT tablets produced by 3D printing. This is a significant step towards personalised drug delivery."

WHAT ARE THE MAIN REQUIREMENTS FOR AN ODT?

As per the US and EU pharmacopoeias, an ODT has to weigh 500 mg (EP, USP) or less, disintegrate in 2 mL available saliva in less than 30 seconds (USP) or 180 seconds (EP) and the friability is to be ≤1% (EU, USP).[1,2,3]

In order to satisfy these requirements, the filler has to create a porous matrix in which the 2 mL saliva will be fast-channelled to the super disintegrant in order to break down within 30 seconds (Figure 1). Mannitol is the chosen filler (but there are other candidates like dextrose, lactose, starch, etc) due to it being water soluble but not hygroscopic (reduce interaction with the water penetration through the matrix pores) and protects actives stability.

WHAT PROCESSES ARE AVAILABLE TO MANUFACTURE ODTS?

Freeze-drying, spray-drying, direct compression, molding sublimation, mass extrusion, and cotton candy are the commonly used methods in the industry. Amongst these, direct compression is the

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most cost-effective and easy-to-handle on standard equipment, resulting in low-friability tablets.

In recent years, the excipients industry has developed a number of ready-to-use ODT platforms by co-processing the filler, usually mannitol, with a superdisintegrant. The platforms include:

- F-MELT® (Fuji Chemical Industries, Tokyo, Japan)
- Ludiflash® (BASF, Ludwigshafen, Germany)
- Parteck® ODT (Merck Millipore, Billerica, MA, US)
- Pearlitol® Flash (Roquette Pharma, Lestrem, France)
- Pharmaburst® (Catalent, Somerset, NJ, US)
- PROSOLV® ODT (JRS Pharma, Rosenberg, Germany)

The main challenge in ODT formulation is the excipients screening in order to find the right balance between disintegration time, friability, API stability and mouth feel. These aspects are explored in greater detail in the case studies that follow.

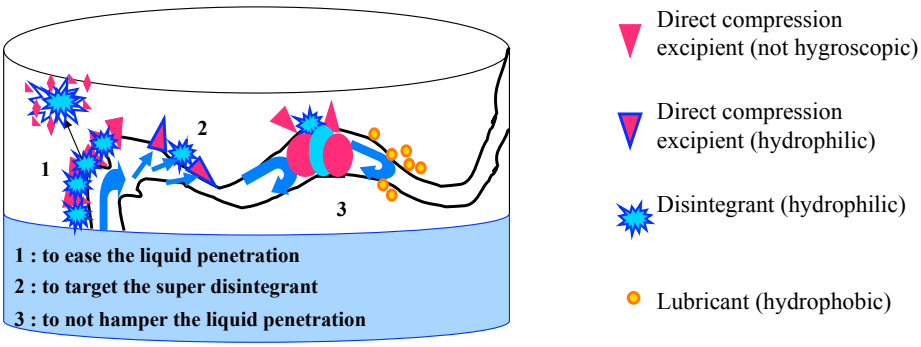

Figure 1: Mechanisms of ODT disintegration.

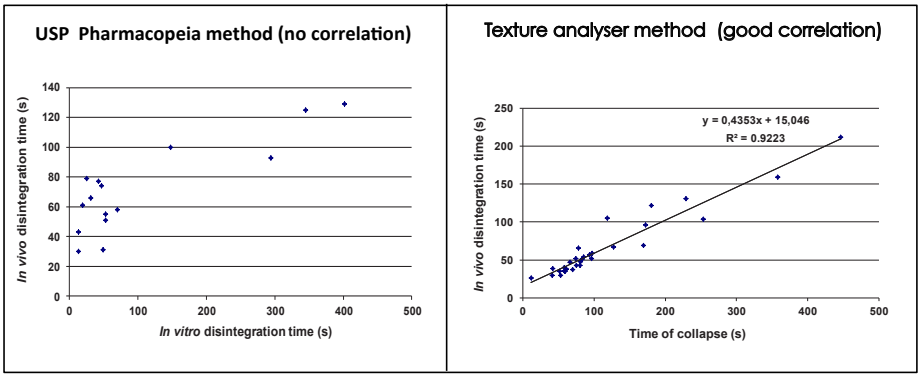

Figure 2 Disintegration time in vitro/in vivo correlation.

CASE STUDY 1

Disintegration-Time Optimisation of Ready-to-Use Platforms

Disintegration time can be evaluated *in vitro* as per the USP/EU Pharmacopoeias' methods or any method using Texture Analyzer and their correlation with *in vivo* evaluation by a taste panel (Figure 2).

300 mg ODT placebos were made using ready-to-use ODT platforms at two hardness values (50 N and 90 N) and their disintegration times were evaluated *in vitro* (Figure 3a & b) and *in vivo* (Figure 3c).

ODT platforms composition filler: disintegrant is as follows: P1 (Mannitol: Starch); P2 (Mannitol: Crospovidone, PVA, PVP, SLS); P3 (Mannitol: Crospovidone, MCC, SiO2, Fructose) and P4 (Mannitol: Croscarmellose).

Tablet hardness has no effect on the disintegration time *in vitro* (both methods Figure 3a and Figure 3b) or *in vivo* (Figure 3c) for P1 while for the other platforms there is noticeable variation as a function of hardness. The reason for P1's short disintegration time resides in the water access (through porous matrix) to the disintegrant due to its superior wettability compared with the other platforms (Figure 4).

CASE STUDY 2

Impact of ODT Platform Composition on Mouth-Feel

24-trained panelists were asked to put an ODT placebo between tongue and palate applying a slight pressure and then their opinion about the mouthfeel was recorded. Mouth-feel is critical in patient acceptance of an ODT (due to its residence time in the buccal area) and is very much linked to attributes such as smooth, creamy, sweet, etc. Unfortunately, for some ODT platforms, the synthetic origin of their components seems to affect their taste and texture negatively. The taste panel evaluation of P1 to P4 commercially available ODT platforms were as follows:

P1: Sweet taste, creamy, smooth and fine texture and off notes (Medicinal)
P2: Creamy and sticky texture and off notes (Dry, Glue, Cardboard, Bitter)
P3: Not very sweet, takes too long time to melt and off notes (Cardboard, Bitter)
P4: Takes too long to melt, hard center and off notes (Cardboard, Chemical)

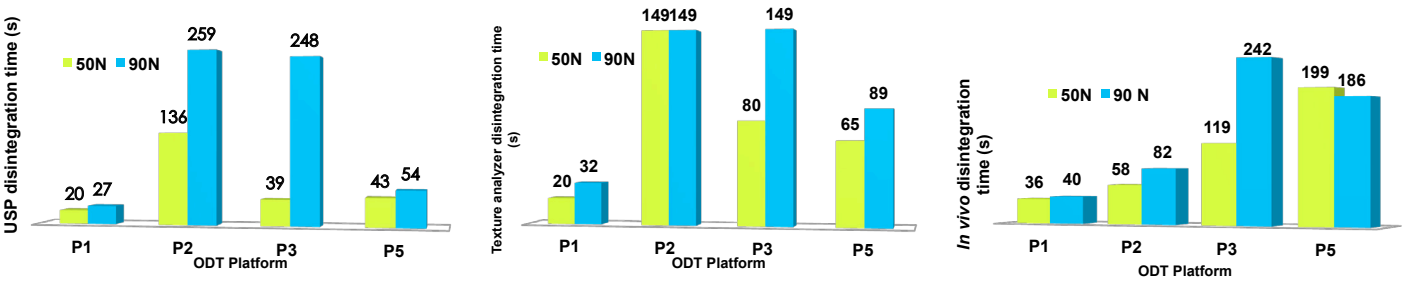

Figure 3: Disintegration times (a) in vitro, using the USP method, (b) in vitro using Texture analyzer method, and (c) in vivo.

CASE STUDY 3

Impact of ODT Platform Composition on Chemical & Physical Stability

ODTs were formulated with 6% benzocaine (as a model drug), 1.5% magnesium stearate, and 92.5% of the respective P1, P2, P3 ODT platforms (as described previously) and P4 (mannitol: xylitol , MCC, crospovidone, Mg alumino silicate, DCP). Each formulation was tableted at 500 mg weight using 10 mm diameter concave punches on a Korsch XP1 research tableting machine under two conditions.

The tablets in the first set were produced at different compression force depending on platform compressibility to create tablets with an average hardness of 100 N. The tablets in the second set were made under a constant compression force of 20 kN, which resulted in tablets with varying hardness. Tablets were evaluated in accordance with US Pharmacopoeia methods for hardness, friability, and *in vitro* disintegration time. Tablets were placed under ICH stability conditions in humidity chambers at 25°C/60% RH or under accelerated conditions, 40°C/75% RH, for up to six months in open pans. Following storage under the various stability conditions, tablets were photographed and their diameter measured. Benzocaine was chosen as a model drug due to its propensity (H2N group) to degrade under certain circumstances (reducing sugars, formic acid, and formaldehyde) and its degradation (Brown Millard reaction, N- Formyl benzocaine, p-amino benzoic acid, amide degradation product) under stability conditions was evaluated by LCMS.

Physical stability was impacted by reducing sugar (fructose), superdisintegrants and MCC (see Figure 5), while chemical stability was impaired by reducing sugar (fructose) and reactive residues (peroxides, formic acid and formaldehyde) in crospovidone, PVP or PVA. P1 and P2 displayed a very good chemical and physical stability.[4]

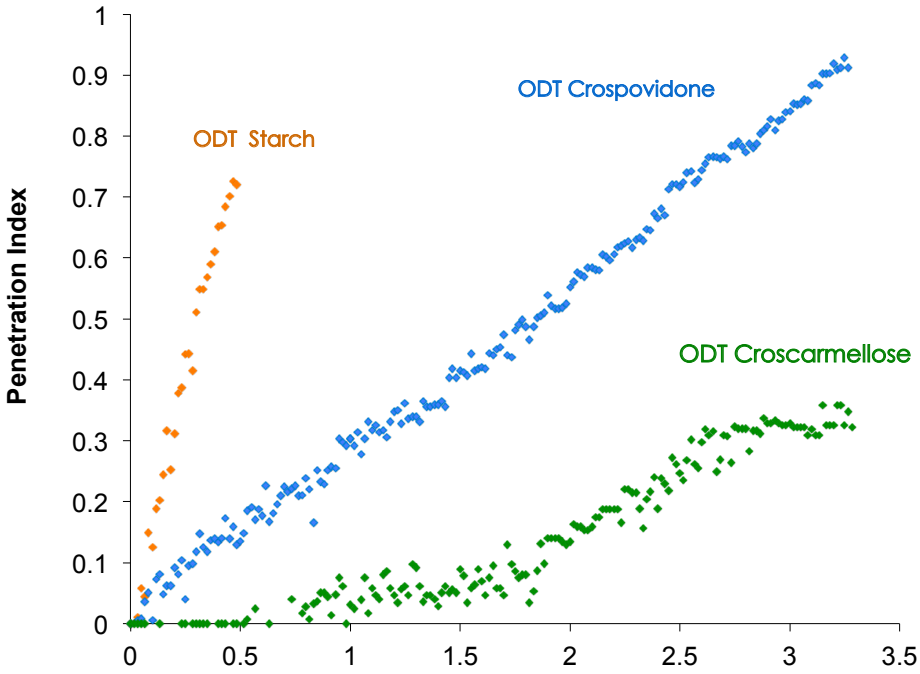

Figure 4: Wettability of ODT platforms with differing disintegrants (P1 has the fastest disintegration due to highest disintegrant wettability).

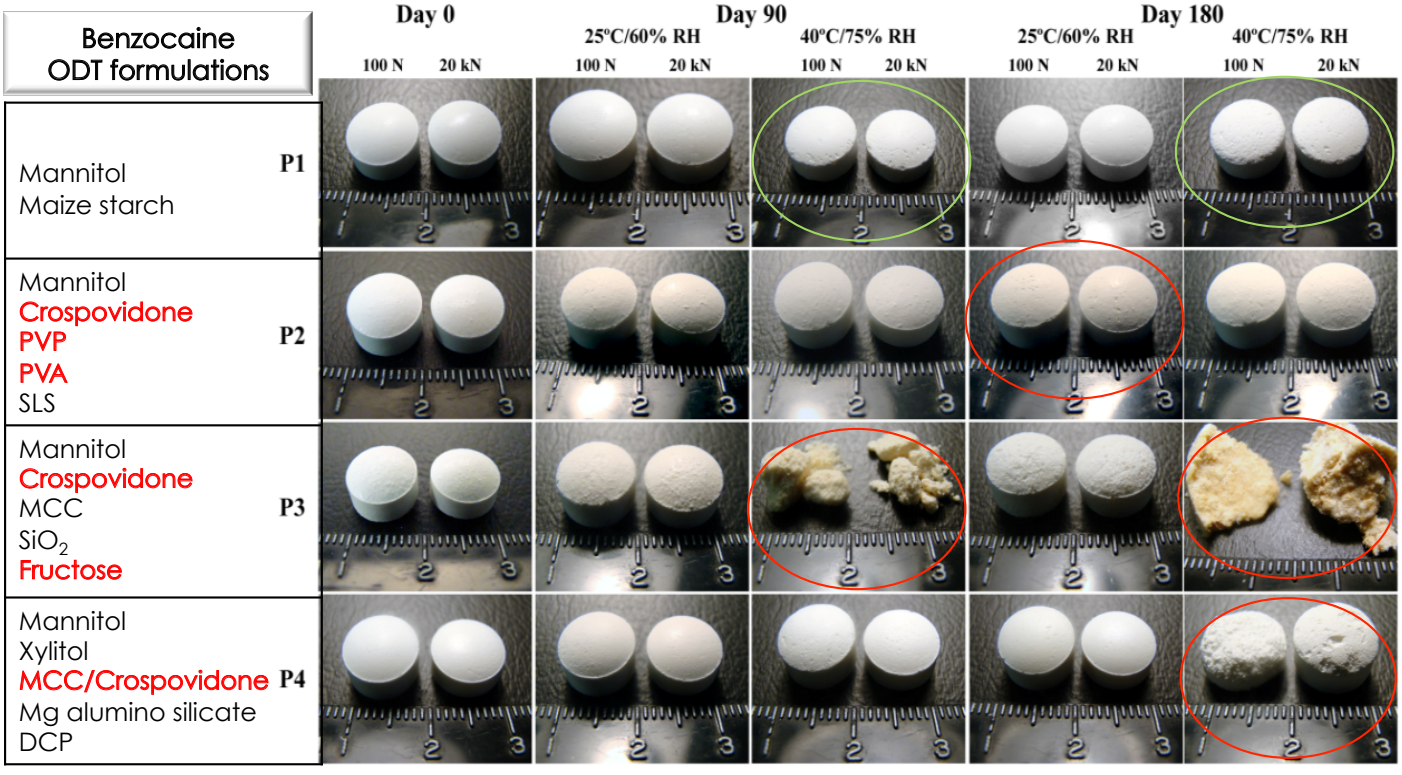

Figure 5: Benzocaine stability study results.

ODT BY 3D PRINTING: A TRANSITION TO PERSONALISED MEDICINE

Recently, the US FDA approved SPRITAM (levetiracetem) ODT tablets produced by 3D printing. This is a significant step towards personalised drug delivery being tailored to the individual patients based on their predicted response or risk of disease. The treatment will be more cost-effective and accurate or, in other words, "therapy with the right drug at the right dose in the right patient".[5]

GIVING PRACTICALITY TO NOVELTY

It is well known that more than 45% of new drug entities have solubility issues, and micronisation/ nanonisation is one way to address this problem. However, reducing the particle size at the micro/ nano scale, the drug is usually delivered only as an injectable. Normally it cannot be formulated as a conventional tablet because, during compression, particles will aggregate resulting in bigger particle size and solubility reduction. However, in the case of ODTs, due to low compression force applied, the particle size is not changed.

For the same reasons, ODTs are potentially very suitable for protein and peptide delivery, preserving their structure, with delivery in the buccal cavity increasing their bioavailability. As the next generation of drugs coming through pipelines are increasingly biopharmaceuticals, ODT represents a viable option for their oral delivery.

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Dr Carmen Popescu holds a BS in Physics and a PhD in Biophysics from the University of Bucharest, Romania. She is a Senior Project Co-ordinator at Roquette America, Inc, and Adjunct Associate Professor with University of Illinois at Chicago, Roosevelt University, and the University of Tennessee. She has published more than 120 research papers, book chapters and presentations on classic and new drug delivery dosage forms for small and large molecules. Additionally she is a reviewer for the International Journal of Pharmaceutics, Journal of Pharmaceutical Sciences, European Journal of Pharmaceutics and Biopharmaceutics, Journal of Pharma & Pharmaceutical Science and an active member of AAPS and CRS.

ACCU-BREAK'S INNOVATIVE TABLET TECHNOLOGY – 2016 ADVANCEMENTS

Here, David Beach, PhD, Technical Consultant, Formulation Development and Manufacturing, Accu-Break Pharmaceuticals, provides a run-down of the company's tablet technologies which, among other benefits, allow patients to split tablets readily and reliably.

Tablet splitting as a means to manage costs, swallowing, titration and dose adjustment could be a better and more efficient alternative if it were easier and less risky.

For example, Accu-Break Pharmaceuticals has developed two worldwide patented distinct multi layer tablet technologies, known as Accu-B and Accu-T, which incorporate a drug-free layer.

> "Compared with a conventionally scored tablet, the Accu-B bilayer design ensures accuracy of dosing of all segments and eliminates concerns over loss of mass during the tablet splitting operation."

ACCU-B

With the Accu-B technology, the dosage form has two layers, one of which is drug free. The second layer contains drug and is deeply scored (see Figure 1). The drug-free layer provides several unique features: first and foremost, given the deep score in the drug layer, the drug-free layer forms a backbone that gives the finished dosage form mechanical strength to withstand packaging and shipping operations. Secondly, the drug-free layer is the fracture plane for the Accu-B tablet. The tablet can be broken through the score and the fracture occurs in the drug-free layer.

Compared with a conventionally scored tablet, the Accu-B bilayer design ensures accuracy of dosing of ALL segments and eliminates concerns over loss of mass during the tablet splitting operation.

Using the Accu-B technology, scored tablets can be made that completely satisfy the testing and data requirements for both the European Pharmacopoeia's Monograph 0478 and the US FDA's 2013 Guidance for Industry, "Tablet Scoring: Nomenclature, Labeling, and Data Evaluation".

The FDA Guidance is intended to:

- Reduce potential risks associated with inaccurate doses resulting from tablet splitting due to uneven drug content, loss of mass, weight variation and/or stability changes
- Ensure consistent scoring, pattern and function between innovator drugs and generic copies
- Allow for "functional scoring" to be included in the product label for Sponsors supplying requisite supporting data.

> "Unique fixed-dose combination tablets can be made where the top and bottom layers contain different actives. In this configuration, the two different drug layers can be separated if desired by splitting the tablet through the middle-drug free layer."

ACCU-T

The Accu-T technology allows for five layers in a taller-than-wide tablet, and the incorporation of drug-free layers to serve one of two purposes.

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One is that the drug-free layer provides a physical barrier between active ingredients. This barrier allows the formulation of incompatible actives with no worries about co-mixing and resultant physical or chemical stability issues. The technology utilises machinery that can produce tablets with up to five compressed layers so the use of more than one drug-free layer can facilitate a "poly pill" with three different API-containing formulations separated by inert/placebo layers.

In the other application, a drug-free breaking layer is incorporated into the middle of an Accu-T tablet and can be used to separate the drug-containing layers. Since the drug-containing layers are physically located at the top and bottom of this taller-than-wide tablet, breaking the tablet through the middle drug-free layer separates the dose into exact halves. The top and bottom layers might contain the same active (Figure 2). Or unique fixed-dose combination (FDC) tablets can be made where the top and bottom layers contain different actives. In this configuration, the two different drug layers can be separated if desired by splitting the tablet through the middle-drug free layer (Figure 3).

Patients taking antihypertensive FDCs, for example, can be confronted with side effects that result from one of the drugs within the FDC, resulting in at best, poor compliance and in many instances prescription discontinuation. With the Accu-T FDC tablet design, a patient could suspend treatment with one of the drugs in the FDC by simply breaking the tablet through the middle drug-free layer. When appropriate, the patient could then resume taking the whole tablet, which allows some dose flexibility without having to stop the prescription entirely.

The tablet could also be used to initiate treatment with a single agent and then add the second therapeutic agent and, thus, efficiently transitioning the patient into a convenient FDC without the need for separate prescriptions during the titration phase.

WHY HAVE FDCS BEEN CRITICISED IN THE PAST?

The largest historical criticism of FDCs has come from the lack of dose flexibility. Taking antihypertensive FDCs as an example, treatment is typically initiated with a single agent, which is titrated to a maximum tolerated dose. If the desired effect on lowering blood pressure is not achieved, a second agent is added, which also requires titration and can lead to lowering the dose of the first agent. A third agent is sometimes added to the mix, or substituted for one of the initial drugs. This process continues until the patient's blood pressure is within the target range, and then the physician looks for an option to transition the patient to an FDC that contains APIs at the effective dose for that patient. This is done of course to simplify the dosing regimen for the patient in an attempt to maintain adherence to the regimen.

Problems arise when a dose adjustment is necessary due to the inflexibility of traditional FDCs. The convenience of a single dosage form is offset by the inability to manage dose adjustments without the need for new prescriptions. If a patient is transitioned to an FDC, inevitably an adjustment will be made to their dose(s), their regimen, the specific drugs being used, or all of the above. So, from that perspective, the criticism is justified. However, for those patients who are effectively managed using FDCs, the ability to take lower doses of two or more medications in a single dosage form is highly desired, especially if it is a once-a-day regimen.

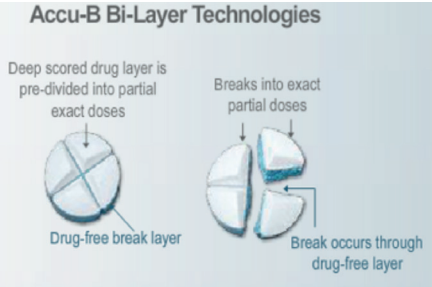

Figure 1: The Accu-B bilayer tablet technology.

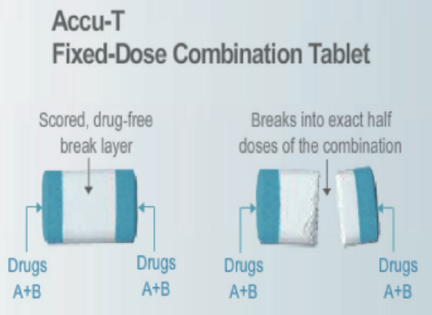

Figure 2: The Accu-T technology configured for a fixed-dose combination.

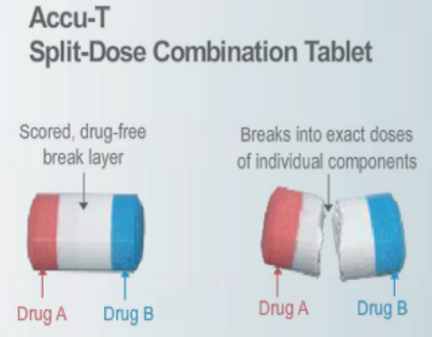

Figure 3: The Accu-T technology configured for a split-dose combination.

FURTHER APPLICATIONS OF ACCU-B

Exploration of the Accu-B type technology for extended-, modified- and sustained-release tablets has produced product with the same release profile as the intact, whole tablet. In the case of a modified-release dosage form, the engineering of the tablet tooling and thus the finished, compressed tablet, is crucial to maintaining the desirable drug release profile. As the deep score of the Accu-B tablet reduces the surface area of the rupture of the active layer when the tablet is broken, achievement of identical release profiles becomes a simple formulation modification of the existing tablet, and in many cases can obviate the need for bioequivalence testing of the Accu-Break dosage form based on identical *in vitro* release profiles. This attribute makes the adoption of the Accu-Break technology attractive for those sponsors seeking patent life extension along with all of the other desirable attributes of the Accu-Break technology portfolio.

ABOUT ACCU-BREAK

Based in Hollywood, FL, US, Accu-Break Pharmaceuticals is a technology licensing and product development company. The company has invented, developed and patented a suite of novel Accu-Break technologies that enable pharmaceutical tablets to be made that can be subdivided by hand into accurate partial doses with the intent of making it easier and safer for patients to adjust their dose. Behind the strength of its innovative inventions and broad patent portfolio, the company is currently developing its first product, and is licensing the Accu-Break technologies to other parties for product development. Accu-Break currently has 58 patents issued and four patents pending worldwide.

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DIAL THE DOSE: A CLEVER DISPENSER FOR NON-STERILE LIQUIDS

There have been several reports and studies which have highlighted the dangers of accidental overdose from using teaspoon- or tablespoon-based instructions for liquid medications. Paul Wismer, MBA, from Balda explains how their product, Dial-the-Dose, can help improve accuracy with liquid dosing.

> "In the US, over 10,000 calls to poison centres occur because the wrong dose of oral liquid medications was given to a child and over 70,000 children visit an ER as a result of medication overdoses.."

Have you ever given a child cough medicine, pain reliever or antibiotics in the middle of the night? Did you measure the dose with a spoon or cup? Besides any difficulties in seeing and/or measuring the dose, how accurate are such dispensing aids, regardless of the time of day? How error-free are users when they dispense the medicines via these dosing aids?

A study of people's behaviour and perception regarding liquid dosing was conducted in the US a few years ago.[1] Many different kinds of dosing errors can occur and, especially with children, the consequences can be very severe. Using a teaspoon or tablespoon, for example, to administer children's medications can often lead to medication dosing errors. Teaspoon- or tablespoon-based medicine instructions doubled a parent's chances of incorrectly measuring the intended dosage, and also doubled the risk they would not accurately follow the doctor's prescription, the study authors found.

"A move to a millilitre preference for dosing instructions for liquid medications could reduce parent confusion and decrease medication errors, especially for groups at risk for making errors, such as those with low health literacy and non-English speakers," said the study's lead author Dr Shonna Yin, an assistant professor of paediatrics at NYU School of Medicine (New York, NY, US).

More than 10,000 annual calls to poison centres occur because the wrong dose of oral liquid medications was given to a child, according to background information included in the study.

In addition, over 70,000 children visit an Emergency Room annually as a result of unintentional medication overdoses.[2]

A number of groups have suggested that paediatricians and pharmacists switch to millilitre dosing for young patients, including the American Academy of Pediatrics, the US Centers for Disease Control and Prevention, and the Institute for Safe Medication Practices.

The FDA provided guidance in 2011 on dosing devices for orally administered liquid medications. Prior to that there was no standard – ML, mL or even cc were used, and sometimes the instructions would differ from those which were actually on the delivery/measuring device.[3]

There have been numerous reports of accidental overdose that were attributed, in part, to liquid measure markings on dosage cups provided with orally ingested OTC

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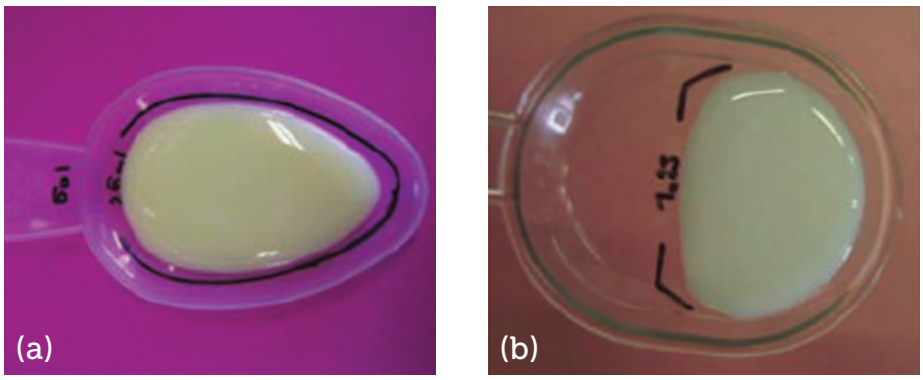

Figure 1: The discrepancy between the nominal and actual volume of different measuring spoons. (a) Difference in volume obtained when measuring a 2.5 ml dose with a pipette compared with the use of the ½ graduation of a measuring spoon supplied with amoxicillin. (b) Difference in volume obtained when measuring a 1.25 ml dose with a pipette compared with the use of the ¼ graduation of a measuring spoon supplied with erythromycin.[4]

Figure 2: Dial-the-Dose.

liquid drug products that were misleading or incompatible with the labelled dosage directions for use. In addition, these difficulties may lead consumers to use less accurate means (e.g. household spoons) to give children medication, leading to under dosing or overdosing. The FDA is especially concerned because orally ingested OTC liquid drug products are frequently intended to be used in paediatric patients.[2]

In another study it was shown that dosing of suspensions using the measuring devices provided with the product may constitute a significant source for the lack of dosing accuracy. The overall results reveal that using the ½ and ¼ graduation marks on the dosing spoon manifest overdosing can be observed (Figure 1).[4]

DIAL THE DOSE SOLUTION

But the question is: what concrete solutions are available to help consumers? Over the years, a number of "dispensing aids" have been developed. Ideally these should be easy to use, yet very accurate, and measuring in mL would be optimal.

Balda has developed one such solution, called Dial the Dose. This simple yet clever liquid dispensing device allows accurate and easy dosing of non-sterile liquid medicines. By simply turning the end of the plunger, you can pre-select the volume (Figure 2). In the example here, there is a 3 mL dispensing capacity, divided into six steps of 0.5 mL each. By pulling the plunger until it stops, it is possible to aspirate exactly the amount "dialled-in". This means there is no need to look at graduation markings on the barrel – it simply needs to be filled and then can be completely dispensed.

The dosing accuracy was measured to be around ±2% with saline. This level of accuracy is more stringent than the FDA requirements.

Dial the Dose is a platform technology. This means other barrel volumes and steps are customisable for the customer's needs. Balda can produce the dispensing devices, on an original equipment manufacturer (OEM) basis, for pharmaceutical or diagnostic customers around the world, providing regulatory support (CE and FDA, for example) as well, so as to support clients in having their product ready for market.

Balda is an expert in injection moulded plastic, and can therefore also design bottle closures with the customised plug and hole concept (Figure 3). Of course, different colours and designs are also possible, giving your product an easily identifiable link to your corporate imaging. But the main goal is clear: easy and accurate dosing to help parents give their children the right dose in a simple manner.

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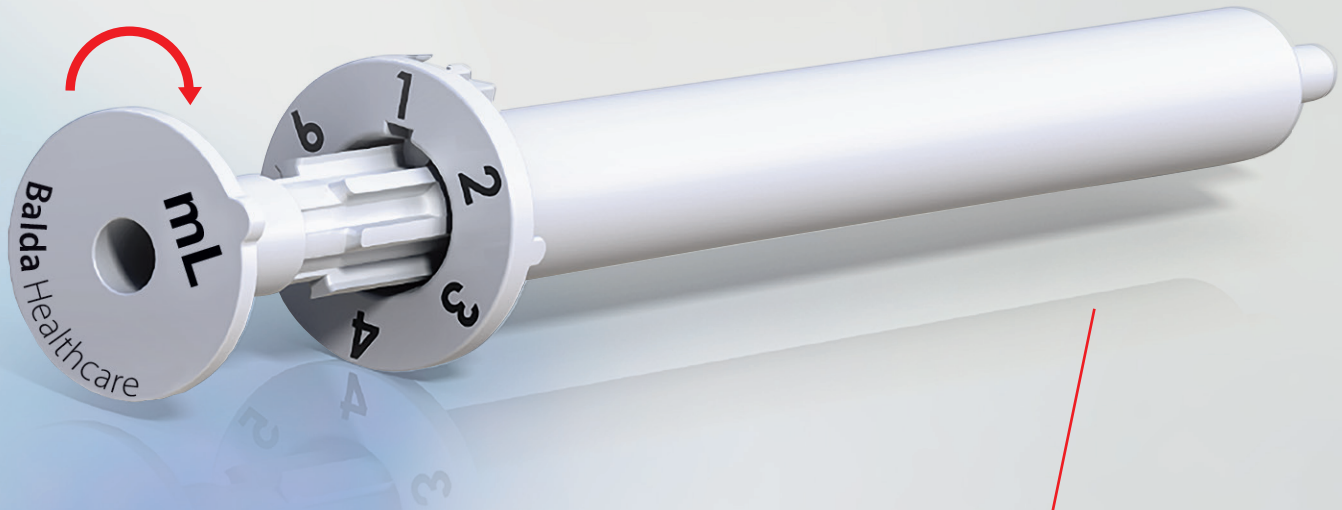
Figure 3: Cap with tailor-made connection to DtD.

Dial the Dose – The Smart Liquid Dispenser

Easy to use yet highly accurate



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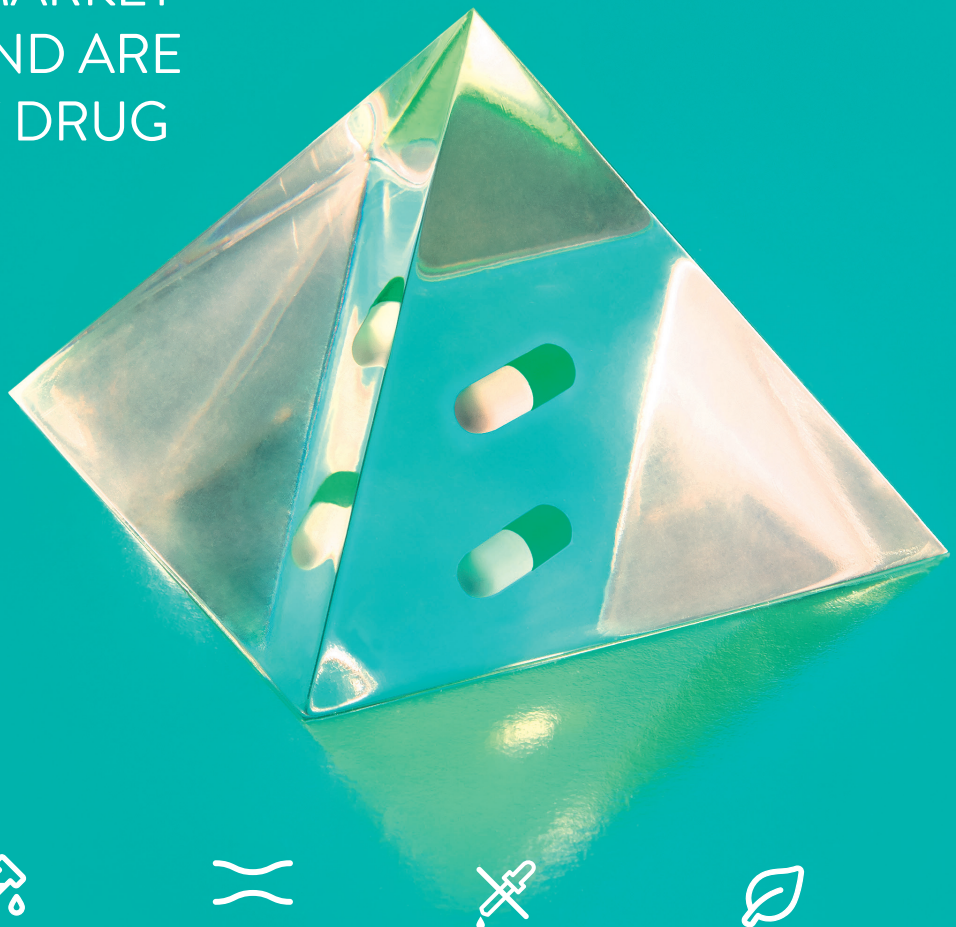

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Publication Month	Issue Topic	Materials Deadline
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October 2016	Prefilled Syringes	August 29th
November 2016	Pulmonary & Nasal Delivery	September 26th
January 2017	Ophthalmic Drug Delivery	November 21st
February 2017	Prefilled Syringes	December 19th
March 2017	Skin Drug Delivery: Dermal, Transdermal & Microneedles	January 23rd
April 2017	Pulmonary & Nasal Drug Delivery	February 27th
May 2017	Injectable Drug Delivery: Devices Focus	March 27th
June 2017	Connected Drug Delivery Systems	April 24th
July 2017	Novel Oral Delivery Systems	May 29th
September 2017	Wearable / High Volume Injectors	July 24th