

NOVEL ORAL DELIVERY SYSTEMS



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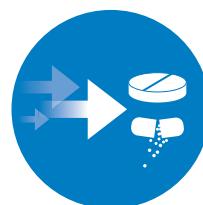
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PREVENTION NOT CURE: AVOIDING A EUROPEAN PRESCRIPTION OPIOID EPIDEMIC

The opioid addiction crisis in the US and Canada is a pressing and immediate problem in today's healthcare landscape. Here, Damon Smith, PhD, Chief Executive Officer of Altus Formulation; Richard Dart, PhD, MD, Executive Director of RADARS System; and Christopher Hirst, Head of RPH Pharmaceuticals, Recipharm, discuss the causes and possible solutions to the epidemic, as well as whether or not Europe is likely to face a similar fate.

PREScription OPIOID ABUSE

In the US, the number of people dying from prescription opioid overdose is shocking. The US Centers for Disease Control and Prevention estimates

that, from 1999 to 2016, over two hundred thousand deaths have occurred this way,¹ in 2016, 46 people died every day.

Some may argue America is a special case and that a prescription opioid epidemic could never happen in Europe. They argue that, in the US, pharmaceutical companies underplayed the addictive properties of opioids and physicians over-prescribed them. In part they may be correct, however such practices are not unique to the US.²

Such marketing tactics also fail to account for Canada's prescription opioid problem. Canada runs a very different healthcare system to the US, yet Health Canada reports that in 2016 there were almost 3000 opioid related deaths,³ which translates to about eight people dying per day. As the Canadian population is 10 times smaller than the US, these figures are alarming. Arguments that Europe is immune to an opioid crisis because of its different prescribing habits must be viewed very critically.

Putting the Genie Back

Both Canada and the US are now implementing multi-focal approaches to address their prescription drug abuse problems. Whilst they are starting from a disadvantaged position, addiction having already taken hold in their populations, evidence supports the new controls are taking effect.⁴

"Canada runs a very different healthcare system to the US, yet Health Canada reports that in 2016 there were almost 3000 opioid related deaths,³ which translates to about eight people dying per day."

In general, the approach being taken in North America is four-pronged:

1. Better physician training and controls on prescribing
2. Increased efforts and treatment options for addict rehabilitation
3. The introduction of abuse deterrent opioid/stimulant formulations, including incentives for generic approaches
4. Increased surveillance to track rates of abuse and monitor for signs of effectiveness.

As Figure 1 shows, Europeans are consuming ever increasing amounts of opioids. Europe has the opportunity to learn from the North American experience and, in doing so, avoid its own opioid epidemic. Without due attention this possibility is a real one, as this article will discuss.

THE NEED FOR EFFECTIVE PAIN CONTROL

In order to address prescription opioid abuse it's essential to understand why such drugs are necessary; attempts to prevent abuse cannot limit access to patients.

Chronic Pain

It is a cliché to point out that we live in an ageing world, but it is evidently true. From 1990 to 2014, the life expectancy for an adult

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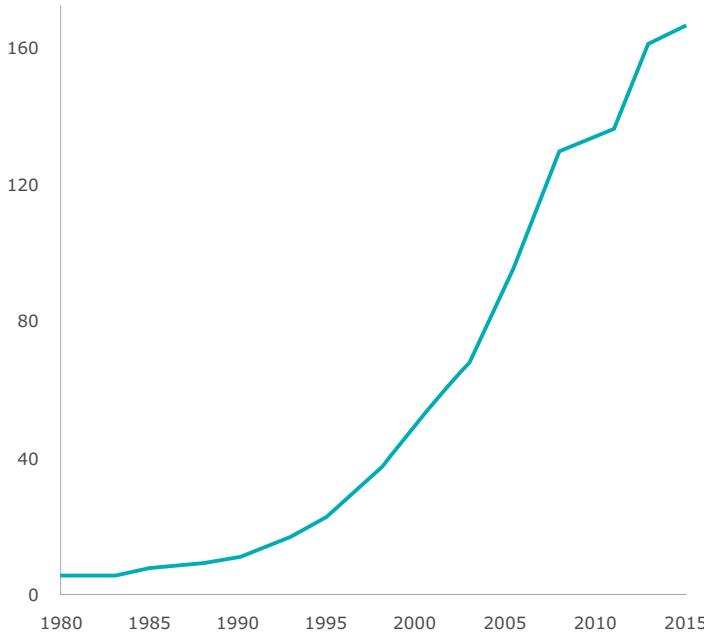


Figure 1: European Total Opioid Consumption 1990-2015 (mg/capita).

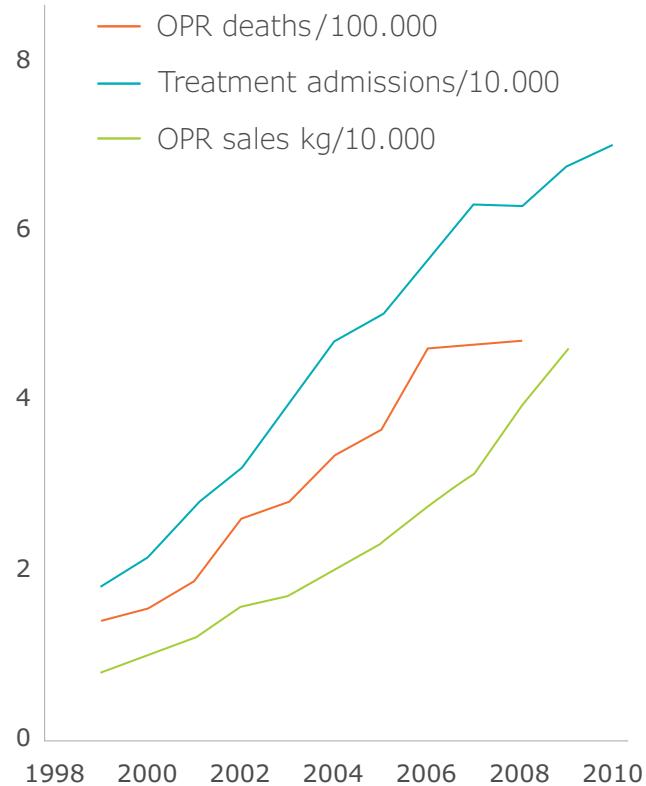


Figure 2: Rates of opioid pain reliever (OPR) overdose death, treatment admissions, and kilograms of OPR sold, 1999–2010.

"When chewing no longer satisfies an addiction, tablets may then be crushed and snorted (insufflation) or crushed and mixed with liquids and injected, a case in which overdose is common."

in the EU grew by some six years.⁵ It is also a cliché that with greater age comes greater pain, but sadly this also is true; approximately 20% of European adults suffer from chronic pain and the prevalence is greater in older people.⁶ If not well treated, chronic pain sufferers are more likely to be depressed, take more time off work and, despite the general upward trend, have a lower life expectancy,⁷ all of which poses a significant societal cost. Effective remedies like prescription opioids are needed to address the growing incidence of chronic pain.

Acute Post-Operative Pain

Similar growth is seen in the number of patients requiring post-operative pain relief. For example, in the UK, approximately

four million surgeries are performed every 12 months, equating to a European total of 45 million operations per year. This number is growing 5.5% annually and 80% of patients experience post-surgery pain requiring analgesia. Opioid narcotics are the most widely prescribed analgesics in this setting today as they offer fast and effective treatment in both inpatient and outpatient settings.⁸

Cancer Pain and Palliative Care

Cancer is typically a later life disease and patients suffering cancer pain, as well as those requiring effective palliative care, frequently rely on oral opioids. In these circumstances, eventually there are no alternative medications.⁹

To conclude, the 10% increase in prescribing of pain medications by German physicians in the last few years is typical of the EU as a whole^{9–12} and reflects the needs our ageing population and changing lifestyles have for effective analgesia.¹³ In many cases there are no alternatives to opioid analgesics, which will be needed in increasing amounts.¹⁴

Opioid consumption in Europe today (Figure 1) is rising at rates seen in North America in the early years of this century. The growing number of calls to

redress these increases are well founded, as the link between opioid sales and deaths from prescription opioid abuse has been conclusively established (Figure 2).^{15–18}

ABUSE DETERRENT FORMULATIONS

The Road to Addiction

The path from abuse of prescription drugs to addiction and death has been described many times. Figure 3 summarises this principle, beginning with susceptible patients swallowing multiple tablets to achieve euphoria. As tolerance and dependence take hold, such behaviours may progress to more dangerous forms of abuse where tablets are chewed before swallowing to release drug more rapidly, an approach to which extended release tablets containing large amounts of drug have been particularly vulnerable. When chewing no longer satisfies an addiction, tablets may then be crushed and snorted (insufflation) or crushed and mixed with liquids and injected, a case in which overdose is common.

"Abuse deterrent formulations, while not eliminating overdose risk, make it harder for overdose to occur."

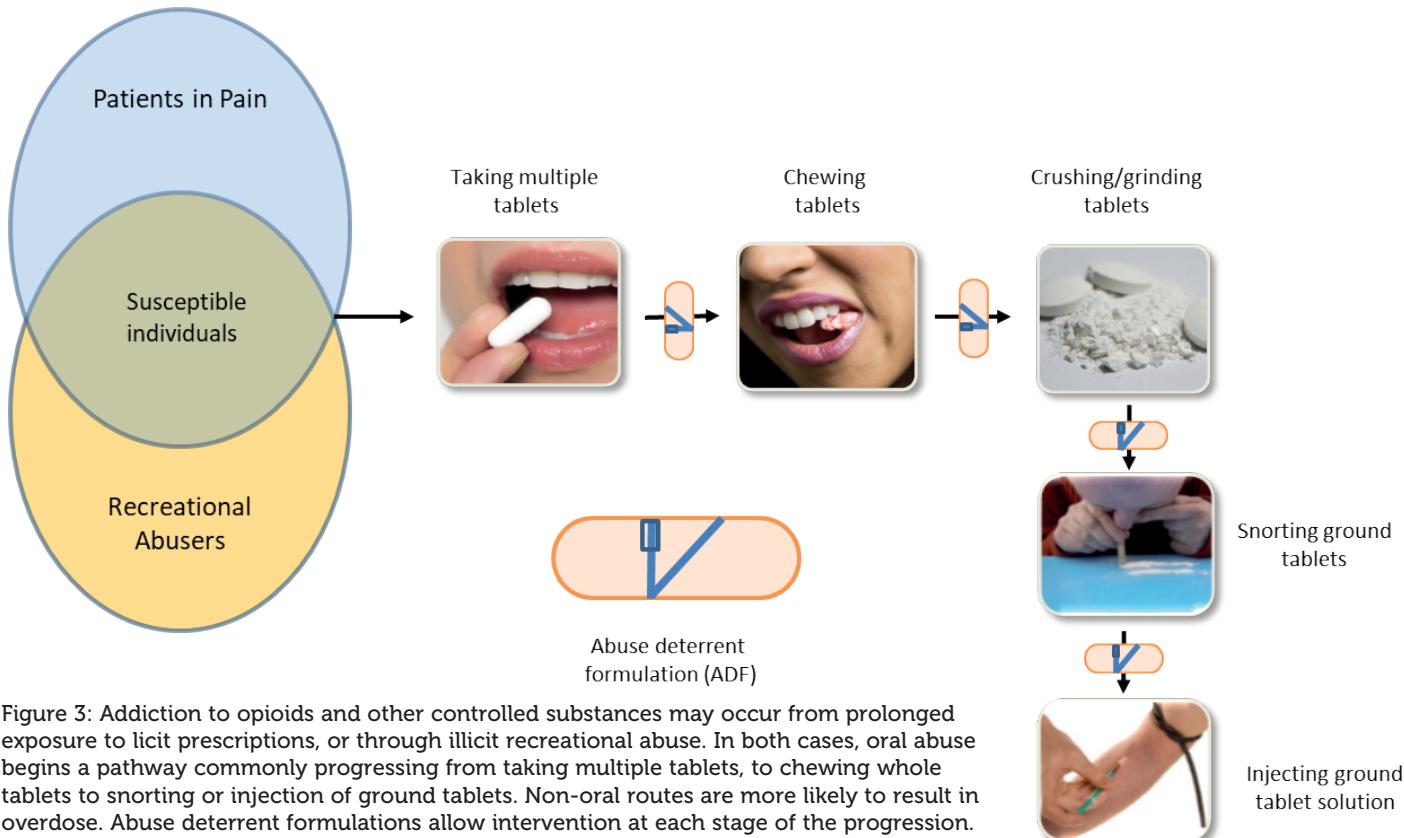


Figure 3: Addiction to opioids and other controlled substances may occur from prolonged exposure to licit prescriptions, or through illicit recreational abuse. In both cases, oral abuse begins a pathway commonly progressing from taking multiple tablets, to chewing whole tablets to snorting or injection of ground tablets. Non-oral routes are more likely to result in overdose. Abuse deterrent formulations allow intervention at each stage of the progression. Early intervention may prevent progression to more dangerous routes of abuse.

Prevention not Cure

Intervening in this progression by reducing the potential for chewing, insufflation and injection provides an opportunity to reduce overdosing and deaths.¹⁹ Such intervention would be especially valuable in the early stages of abuse, i.e. as a preventative measure to avoid addiction rather than as a cure for the addict. Abuse deterrent formulations (ADFs), while not eliminating overdose risk, make it harder for overdose to occur. In principle they employ two basic approaches:

1. Physicochemical Barrier Technologies
 - Here, tablets are hardened to make them difficult to chew and resistant to crushing and grinding. Realising that no technology is immune to such attempts, technologies may also include excipients that swell in the presence of liquids to form a viscous gel that reduces the potential for injection.

Examples of such technologies include heat-treatment recrystallisation (HTR), used on reformulated OxyContin® (Purdue Pharma, Stamford, CT, US), DETERx®, employed by Collegium Pharma (Canton, MA, US), and INTELLITAB™, developed by Altus Formulation (Figure 4).

2. Agonist/Antagonist Technologies
 - In this case, formulations comprise

a separate antagonist included to counteract the effect of the opioid narcotic should the tablets be tampered with prior to ingestion. Whilst these products do not prevent the abuse *per se*, they are nevertheless designed to prevent harmful outcomes should abuse occur.

Examples of products using this approach include Embeda®, a morphine sulphate/naltrexone formulation marketed by Pfizer, and Targiniq®, an oxycodone/naloxone formulation developed (but never marketed) by Purdue Pharma.

Seat Belts for Tablets

ADFs can be thought of as similar to seat belts, i.e. a simple to use, effective technology that makes any vehicle safer to use. This is due to three factors:

1. Effectiveness – Experience has proven seat belts to be effective and the same can be said of ADFs. For example, Severtson *et al*²⁰ and Dart *et al*²¹ report,

amongst other positive trends, that introduction of HTR barrier technology resulted in a reduction of 75% in the number of intentional abuse cases presenting to poison control centres and a reduction of 87% in the amount of non-oral abuse of the product.



Figure 4: The hard, coloured gel that forms immediately when Intellitab™ tablets are ground and added to liquids.

"Opioid narcotics, while a critically important case, are not the only drug that could benefit from an ADF approach, for example the popular press has recently highlighted abuse of gabapentinoids and benzodiazapines."

2. Simplicity – All abuse deterrent formulations are simple to use since, in appearance and administration, they are identical to any other tablet. Simplicity must also extend to manufacturing, as simpler processes lead to lower costs. Barrier technologies which eschew the two active ingredients required by agonist/antagonist formulations may have the advantage here.

3. Cost – The North American experience has shown us that branded ADF products are not easily affordable with prices of US\$20 (£15) per tablet and above being commonplace. Such pricing will likely prohibit the introduction of ADFs and their benefits to the European market. In our view, an ADF formulation should cost little more to the payer than a non-abuse deterrent formulation so that access can be assured. As championed by the US FDA, the introduction of value-added ADF bioequivalents to currently marketed products would be a simple first step in providing safer-to-use tablets to patients, without opening the door to excessive pricing, so long as such products were clearly differentiated in their labels. New regulation to ensure any new drug with abuse potential is formulated with abuse deterrent technology from the outset would be a logical follow up, which would enhance and encourage innovation.

THE NEED FOR EFFECTIVE MONITORING – MOSAIC SURVEILLANCE

Effective surveillance is mandatory for effective tracking of any regulatory strategy. In the case of prescription drug abuse, it is needed both to monitor the benefit (or otherwise) of any new ADF product and to track the emergence of new drugs that would benefit from ADF technology to mitigate their abuse potential. Opioids, while a critically important case, are not the only drug that could benefit from an ADF approach. For

example, the popular press has recently highlighted abuse of gabapentinoids and benzodiazapines.

In the US pre- and post-marketing surveillance of opioid medications has led to the approval of new products by the FDA and, just as importantly, the removal of products because of their abuse potential.²² In Europe, however, the lack of such mosaic systems providing accurate, immediately available, geographically relevant, product-specific information is a hindrance both to understanding the extent of abuse in member states and to effective prevention. Multiple input mosaic surveillance systems, for example comprising data streams from the criminal justice system, treatment professionals, susceptible patient populations and acute health events, in parallel with the cost-effective introduction of ADFs, represent an invaluable tool to combat prescription drug abuse and prevent repetition of the North American experience in Europe.

CONCLUSION

Whether or not Europe has an opioid problem may be debated, as Europe lacks the surveillance systems to monitor this adequately. What is clear, however, is that increases in the rates of opioid consumption are tracking those seen in North America and the potential for increased abuse is therefore present and growing. The introduction of ADFs as a preventative measure to mitigate the potential for abuse offers a cost-effective approach to minimise the human and societal costs of abuse. Linked with effective surveillance we believe such measures should be adopted sooner rather than later.

ABOUT THE COMPANIES

Altus Formulation is a Montreal-based pharmaceutical company that invents and develops new enabling technologies and drug products which it then licenses to its various partners around the world.

The Altus model is to develop patent protected, safer to use "Value Added Medicines" with a special focus on increased patient access especially in the areas of pain/CNS and oncology.

RADARS® System (Researched Abuse, Diversion and Addiction-Related Surveillance) is a surveillance system that collects product- and geographically specific data on abuse, misuse, and diversion of prescription drugs. Post-market surveillance is performed in the US, Canada, UK, Germany, France, Spain, Italy and other countries.

Recipharm is a leading contract development and manufacturing organisation (CDMO) in the pharmaceutical industry, employing around 5000 people. Recipharm offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, and pharmaceutical product development. Recipharm manufactures several hundred different products to customers ranging from big pharma to smaller research and development companies.

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Damon Smith, PhD, is the CEO of Altus Formulation, which he founded in 2013. Prior to Altus, Dr Smith held senior research and development positions in biotech and pharmaceutical companies in the UK and Canada.

Richard Dart, MD, PhD, is the Director of Rocky Mountain Poison and Drug Center, Executive Director of the Researcher Abuse, Diversion and Addiction Related Surveillance (RADARS®) System, and a professor at the University of Colorado School of Medicine.

Christopher Hirst is Head of RPH Pharmaceuticals AB, a subsidiary of Stockholm-headquartered CDMO Recipharm AB. Mr Hirst has held business development and commercial roles at Recipharm, with a focus on generic and value-added medicines.

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HIGH SHEAR COATING: A VERSATILE TASTE-MASKING PROCESS

In this article, Cécile Morin, Technical Communication Executive, Pharmaceuticals, and Yvonne Rosiaux, PhD, Innovation Application Manager, both of Gattefossé, discuss taste-masking, covering the advantages of Precirol® ATO 5 and how Gattefossé's high shear coating process presents an appealing alternative to standard fluid bed techniques.

INTRODUCTION

Many processes exist to circumvent the bad taste of drugs (Figure 1). As such, the challenge for formulators looking to taste-mask a drug is finding the most appropriate method to do so.^{1,2}

The process of coating a drug consists of building a physical barrier onto the drug particles with a film coating, which can be polymer or lipid based. The coated particles

can then be used in sachets or capsules, or transformed into tablets.

The primary advantage of using a lipid-based coating over polymer-based one is that, with lipids, organic solvent and water are absent during the coating process. The preferred lipid for this coating process is Precirol® ATO 5 (glyceryl distearate), due to its moderate melting point and rapid recrystallisation. Moreover, it has US FDA GRAS status and precedent for use, including in paediatric dosage forms.

Using a fluid-bed coater for lipid coating is a well-known technique.^{3,4} The process consists of fully melting Precirol® ATO 5 and spraying it on the drug

"The results of the human taste panel corroborate with drug dissolution and confirm that both processes are efficient for taste-masking KCl."

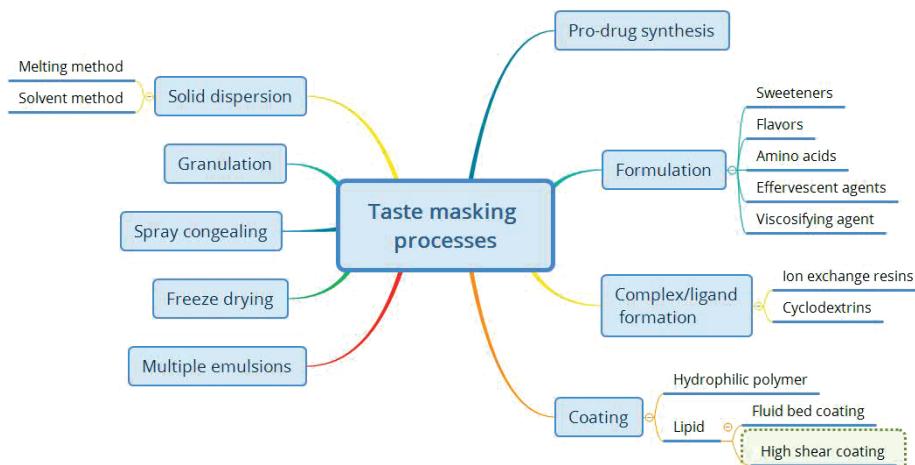


Figure 1: Different taste-masking processes.



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particles. However, insulation of the pipes and the nozzle is required to prevent early lipid crystallisation. As such, Gattefossé aimed to develop a simpler process for taste masking, using a standard high shear coater and Precirol® ATO 5, whereby partial melting of the lipid excipient is driven by sufficient friction of the powders in the bowl, obtaining a thin and homogeneous film around the drug particles.

A SIMPLE PROCESS

For this new taste-masking process, Gattefossé used:

- A conventional high shear coater, without an external heating or cooling system
- A simple binary formulation of 80% API and 20% Precirol® ATO 5.

The high shear coater is equipped with an impeller and a chopper. The impeller drives the powders in the bowl into motion and, at high speed, generates inter-particle friction, thus producing heat. This heat then partially melts the Precirol® ATO 5, which covers the drug particles. During the process, the chopper prevents agglomeration of the particles.

There are four steps in this process:

1. The binary mixture of 80% API and 20% Precirol® ATO 5 is homogenised at low impeller speed (50 rpm) for three minutes at ambient temperature.
2. The impeller speed is increased to 900 rpm, generating friction and heat. When the process temperature reaches 45°C, impeller speed is reduced to 450 rpm and the chopper is started (500 rpm).
3. Once the process temperature reaches 48°C, effective particle coating with the partially molten lipid begins. Coating lasts 3 minutes.

HSC conditions	FBC conditions
<p>Binary formulation 80% KCl/20% Precirol® ATO 5</p> <p>High shear blender (Diosna P1), 1 L bowl</p> <p>Mixing of drug and Precirol® ATO 5 at 50 rpm for 3 min.</p> <p>Generation of friction heat with high impeller speed (900 rpm) until the product temperature reaches 45°C.</p> <p>Coating for 3 min at 48°C; impeller speed: 450 rpm; chopper speed: 500 rpm.</p>	<p>Binary formulation 80% KCl/20% Precirol® ATO 5</p> <p>Top-spray fluid-bed coater (GPCG 1.1, Glatt)</p> <p>Fluidisation of the drug powder for 10 min until the product temperature reaches 42°C.</p> <p>Precirol® ATO 5 is melted, maintained at 100°C and sprayed</p> <p>Spray rate: 10 g/min</p> <p>Atomisation air: 100°C</p> <p>Atomisation pressure: 2.5 bar</p> <p>Air flow rate: 18 m³/h</p> <p>Spray nozzle diameter: 0.8 mm; lowest position</p>

Table 1: HSC and FBC process conditions for KCl coating.

4. The process is subsequently cooled down by simply reducing the impeller speed to 50 rpm, to reduce friction, and chopper speed to 100 rpm, to prevent pack formation. Consequently, the temperature decreases leading to the recrystallisation of the lipid on the surface of the drug particles. At 35°C, Precirol® ATO 5 is fully recrystallised in a solid and homogenous film. The coated particles are then removed for further characterisation and processing into finished dosage forms.

The ideal coating temperature is 48°C. At this temperature about 15% of Precirol® ATO 5 is in a molten state. If the temperature exceeds 48°C, caking or granulation of particles may occur due to a higher fraction of molten lipid excipient, leading to granules.

AN EFFICIENT PROCESS

To demonstrate the efficiency of high shear coating (HSC) versus fluid bed coating (FBC), Gattefossé used KCl as a model drug.

KCl has a strong bitter and salty taste. The process conditions are described in Table 1.

Scanning electron microscope (SEM) pictures of pure versus coated KCl particles (Figure 2) show effective coating with both HSC and FBC techniques. Before coating the particles exhibit cubic structures with sharp edges. After HSC, particles have rounded edges due to the lipid coating. With FBC, the coating is less smooth than with the high shear process.

To demonstrate that high shear coating is masking the taste of the drug effectively, Gattefossé used two assays: a dissolution test and a human panel assessment.

The taste perception threshold for KCl is 0.03 M,⁵ corresponding to 2.2 mg/mL. Drug dissolution exceeding this limit is indicative of KCl's bad taste being detectable, i.e. an ineffective taste-masking process. The drug dissolution was assessed for five minutes in 3 mL at 37°C. Both HSC and FBC were shown to be efficient taste-masking processes since the released drug was well below the taste detection threshold (Figure 3).

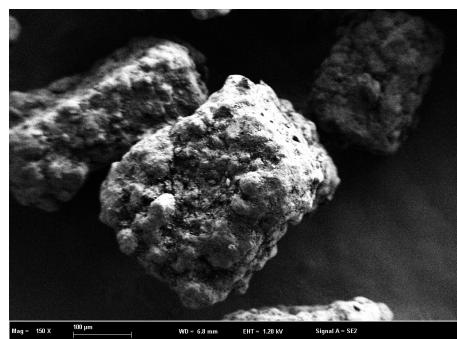
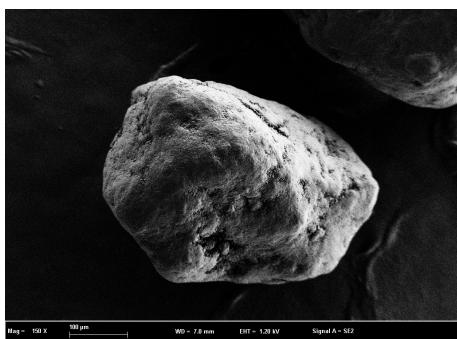
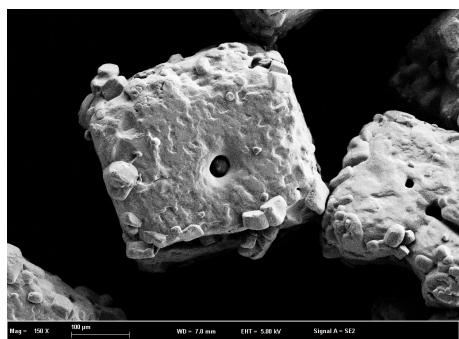


Figure 2: SEM pictures of uncoated and coated KCl particles (magnification: 150). Left: Uncoated KCl; Middle: HSC KCl particles; Right: FBC KCl particles.

"For drugs generating high friction, the impeller speed must be reduced from 900 to 450 rpm when the temperature reaches 42°C (instead of 45°C). This prevents exceeding the ideal coating temperature of 48°C."

A human taste panel evaluated the uncoated and coated KCl particles using a standardised procedure. The different attributes and their definitions used for the sensory evaluation are listed in Table 2. Each attribute was scored on a scale from 0 (best) to 10 (worst).

The assessors placed the test product on the middle of their tongues. Initial impact was assessed immediately. For the next 20 seconds, assessors ranked the taste, flavour and mouthfeel. After rinse off, aftertaste and afterfeel were scored.⁶

Both processes were demonstrated to be efficient methods for taste masking. They dramatically reduced the unpleasant initial impact, the salty and bitter taste and generally had a positive impact on mouthfeel and aftertaste (Figure 4).

The results of the human taste panel corroborate with drug dissolution and confirm that both processes are efficient for taste-masking KCl.

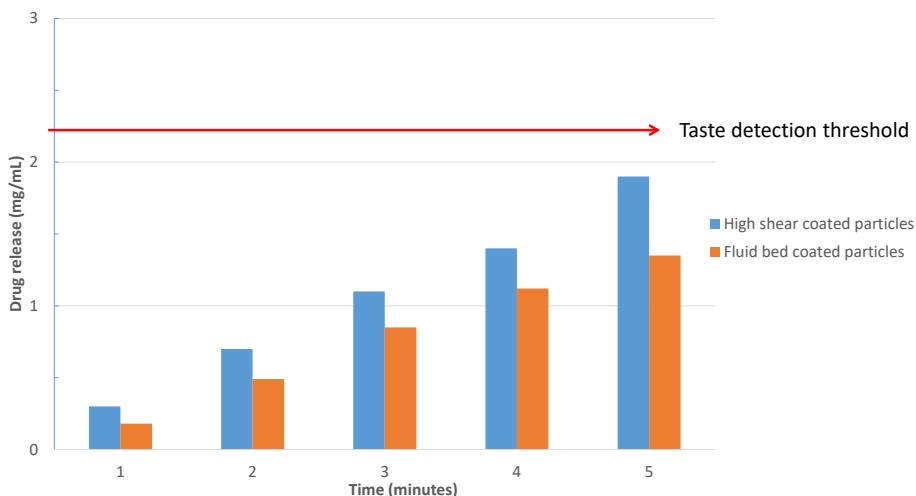


Figure 3: Drug release from coated KCl particles below the taste detection threshold.

Attribute	Modality	Definition
Initial impact	Initial taste, flavour and mouthfeel	The combined intensities for all perceived tastes/flavours/mouthfeels
Salty	Taste/aftertaste	The basic bitter taste associated with NaCl
Bitter	Taste/aftertaste	The basic bitter taste associated with caffeine
Tongue numbing	Afterfeel	A feeling of decreased or loss of sensation on the tongue
Gritty	Mouthfeel	Amount of gritty/grainy particles in the mouth
Tingling	Mouthfeel	A tingling and burning sensation on the tongue and mouth
Astringent	Mouthfeel	A drying, puckering and shrinking sensation in the oral cavity causing contraction of body tissues.

Table 2: Descriptive vocabulary and definitions used by the assessors.

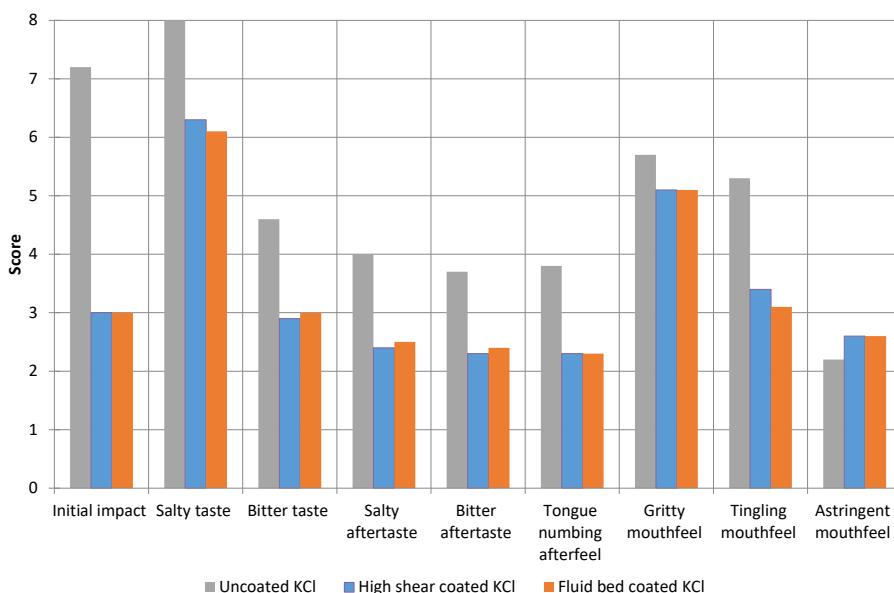


Figure 4: Human taste panel assessment.

A VERSATILE PROCESS

To assess the versatility of the HSC taste-masking process, different APIs were coated (Figure 5). Although the particles were very different in crystalline shape, melting point, mean diameter, particle size distribution and density, they were successfully coated with this process.

It was observed that the generation of friction heat depends on the drug's physical properties (density, size, shape). Particles with high density and large contact surface area generate more friction heat than particles with low density and small contact surface area.

For drugs generating high friction, the impeller speed must be reduced from 900 to 450 rpm when the temperature reaches 42°C (instead of 45°C). This prevents exceeding the ideal coating

Drug	KCl	Isoniazid	Paracetamol	Ranitidine HCl
Crystalline structure				
Melting point (°C)	770	171	169	140
Mean diameter (µm)	370±150	205±130	100±100	330±220
Particle size distribution				
Density (g/mL)	2.0	0.7	0.3	0.6
Time to reach 42–45°C (min)	25	11	48	21

Figure 5: Properties of the different drugs used for taste masking.

temperature of 48°C. Granulation before initiating the HSC process is recommended for particles with low density and small contact surface to reduce the time required to reach 42–45°C. This was the case with the paracetamol grade used.

SUMMARY

Taste-masking with the HSC process presents many advantages over other techniques due to the following factors:

- Use of conventional equipment
- Absence of organic solvents or water in the formulation and during the process
- Low temperature
- Limited number of process parameters to control.

In conclusion, it is a very simple process with a proven efficiency in different model drugs.

ABOUT THE AUTHORS

Cécile Moran is a food engineer with a long experience in communication in the areas of food, pharmaceutical and cosmetic ingredients. At Gattefossé, she is in charge of print and digital communication for pharmaceuticals.

Yvonne Rosiaux obtained her PhD in pharmaceutical technology in 2011 at the University of Lille, France. At Gattefossé her role is to pilot the application laboratory programme in solid oral dosage forms, which covers solubility and bioavailability enhancement, modified release and taste-masking, among others. Her team investigates the performance of lipid excipients in processes such as hot melt extrusion, melt coating, melt granulation etc.

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ORAL FILMS – A MULTI-FACETED DRUG DELIVERY SYSTEM AND DOSAGE FORM

Oral films are a relative newcomer to the drug delivery space, though one with considerable potential. Here Rob Davidson, Chairman and Chief Executive officer, and Jessica Rousset, Chief Operating Officer, both of CURE Pharmaceutical, give an overview of this dosage form, from formulation through manufacturing to future outlook.

INTRODUCTION TO ORAL FILMS

In the late 1970s, rapidly disintegrating drug delivery systems were developed as an alternative to capsules, tablets and syrups for patients who experience difficulty swallowing – a large swath of the population estimated to be between 30–40%.¹ Oral films represented a later advance on this idea, using water soluble polymers that release the medication into the oral cavity. Early oral films had many limitations, such as dosing limited to 30% w/w of medication, difficulty combining multiple active ingredients and poor stability.

One of the earliest pharmaceutical oral films on the market was the Chloraseptic® relief strips for the treatment of sore throat, which delivered a low dose of benzocaine. Shortly after the introduction of Chloraseptic oral film in early 2003, other oral films entered the market but were plagued by stability and packaging problems. Over the last decade, the science behind oral films has advanced significantly with improved methods for testing the purity, potency and uniformity of films, leading to greater investments and commercial viability. There are now a handful of prescription films on the market for the treatment of Alzheimer's, Parkinson's tremors, chemotherapy and radiotherapy induced nausea and vomiting, opioid dependence and pain.

"Over the last decade, the science behind oral films has advanced significantly with improved methods for testing the purity, potency and uniformity of films, leading to greater investments and commercial viability."

ADVANTAGES AND LIMITATIONS

In addition to providing an alternative for populations that have trouble swallowing, oral films can impact a drug's therapeutic index by increasing effectiveness and reducing side effects. Depending on where the film is placed within the oral cavity – on or under the tongue, or against the cheek – release of the drug will differ. When placed against the cheek or under the tongue, contact with saliva or buccal mucosa initiates direct absorption of the drug into the vasculature, avoiding its degradation in the acidic environment of the stomach, gut-wall elimination and hepatic elimination. Drugs administered *per os* that cause significant gastrointestinal side effects can benefit from being formulated as buccal films. Drugs that are pH sensitive may also benefit from buccal delivery using oral film.

Drug dissolution is an important parameter affecting adsorption. When placed on the

"When placed against the cheek or under the tongue, contact with saliva or buccal mucosa initiates direct absorption of the drug into the vasculature, avoiding its degradation in the acidic environment of the stomach, gut-wall elimination and hepatic elimination."



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Figure 1: The film and liner exit the oven and are stored as master rolls, ready to be divided into daughter rolls and further into single doses.

tongue and swallowed, the oral film can be made to disintegrate rapidly, releasing the medication that has been solubilised within the matrix. For extended and intestinal release, encapsulating the drug within the film will protect it from low stomach pH. Oral films present significant advantages for delivering biopharmaceutical classification system (BCS) type II drugs – high permeability, low solubility.

As with any dosage form, oral films present certain limitations. For example, films cannot currently deliver doses in the gram range whilst retaining their rapid release properties and remaining palatable. For lower potency drugs, multiple units of film can be taken to deliver the target dose, which is a feasible solution given the ease with which an oral film is administered. While buccal delivery holds potential for macromolecules, small molecules have been the focus for oral films. Various challenges relating to the excipients and the manufacturing method used will need to be overcome to be commercially viable.²

With the polymer systems typically used, oral films are generally hygroscopic in nature. Therefore, drugs that are susceptible to hydrolysis, such as acetylsalicylic acid, are not good candidates for oral films. The moisture content in the film can be

controlled with appropriate packaging. Encapsulation methods can be used to protect from heat degradation, which may occur during the manufacturing process.

APPROACHES TO ORAL FILM FORMULATION

The design of a thin film formulation is driven by the target product and drug release profile. The primary component of an oral film is the polymer blend or binder, the selection of which should be guided by the desired strength and stability of the film, as well as muco-adhesiveness, pliability, dissolution rate and moisture content. Plasticisers, such as glycerol, are used to improve elasticity of the film, which can be important for manufacturing scale-up. Plasticisers also play a role, when combined with certain polymers, in the overall dissolution rate of the film; some films may need to dissolve over a period of hours and others within seconds depending on the indication. Surfactants are used as wetting, dispersing and solubilising agents for rapid release of the drug in the mouth. Lipids may be used for stabilising hydrophobic drugs. For buccal films, permeation enhancers should be considered, as well as multilayer films with an occlusive layer that prevents

the released drug from being swallowed. Of course, sweeteners, flavourings, bitter-blockers and colouring agents are important for the patient experience.

For most manufacturing methods, solvents play an important role in film formulation for solubility of the molecule within the film forming matrix. Solvents are chosen based on the drug's solubility. The preference is for volatile class 3 residual solvents, such as ethanol and acetone, and non-volatile solvents, such as water. The order in which the various components are admixed is important to optimise to achieve the desired product specifications.

SCALE-UP AND MANUFACTURING CONSIDERATIONS

Scale-up of oral film production involves migrating from a discontinuous process to a continuous one. Several methods for manufacturing an oral film may be pursued depending on the physico-chemical properties of the active ingredient and the target dose,³ but the most common is solvent casting. Using this method, the manufacturing process starts by dispensing the excipients, active ingredient and solvents in a defined order into a temperature-controlled tank and blending them into

"With respect to the popular concept of personalised therapy, oral films provide the unique ability to dispense an individualised dose of medication precisely."

a slurry, typically using a high shear mixer, thus ensuring a homogenous slurry. However, high shear mixers should not be used in the case of encapsulated drug active, as the process will remove the encapsulant. Homogeneity of the slurry should be tested by sampling at different locations in the tank and measuring viscosity and solids content. Depending on the properties of the slurry (i.e. bacteriostatic, bactericidal or growth promoting), in-process bioburden testing may be required. To ensure flexibility in production scheduling, optimal conditions for storing the slurry should be tested.

The slurry is then fed into an oven through a coating station, typically using a pump system. The slurry is applied to a liner using a slot die or knife-over-roll coater, at a determined pin gauge. The selection of the liner is an important consideration in the scale-up process as it will affect how the solvent, usually water, will evaporate. Relevant parameters when selecting a liner are moisture content of the cast film, the location of the heat source and the directionality and strength of the air flow within the oven. It is generally preferred to "bake" the film rather than "broil" it.

Casting parameters – oven temperature, pin gauge and belt speed – required to meet product specifications at the terminal end of the oven should be optimised to achieve the fastest belt speed for highest throughput and cost efficiencies. Some oven systems enable the operator to control the height and directionality of the air nozzles and offer modular heat zones (e.g. infrared, progressive temperature increase). Oven lengths can range from 3.0 m to 7.3 m, or more. The film and liner are then packed as master rolls at the terminal end of the oven (Figure 1, previous page) and should be stored in a temperature and humidity-controlled environment, due to the aforementioned tendency of oral films to be hygroscopic. Stability of the intermediate

"The manufacturing of oral films is a continuous but modular process that is suitable for automation."

master rolls over time should be established by evaluating API content, moisture levels, physical characteristics, pliability and tensile strength. Typically, oral film products are stable at room temperature in an appropriate container closure system. Of note, there is no official method or monograph in the US Pharmacopeia for evaluating oral film properties such as disintegration, dissolution or mucoadhesion.

PACKAGING AND DISTRIBUTION

The final step in production is cutting the master roll into daughter rolls and further into single doses which are then placed into individual pouches or sachets by converting and packaging machines. The API dose of an oral film product is directly informed by its weight. It is therefore critical to control the weight of each film product that is packaged. The size to which each individual film should be cut must be determined during process development to ensure the product meets the target weight and API load. A significant advantage with this dosage form is the ease with which multiple stock keeping units (SKUs) can be produced, simply by modifying the size of the film.

Metalled polyester is a suitable primary packaging material for oral films. It is cost effective and protects the product from moisture and light. This pouch material can be child resistant and closure systems can be designed to ensure the product passes child resistant testing, whilst remaining user friendly for the patient. The pouches or sachets offer larger printable 2D areas, which traditional drug product formats do not. This allows the manufacturer to adapt to rapidly evolving labelling and regulatory requirements for information and anti-counterfeiting, such as product serialisation. Furthermore, the primary package provides sufficient space to include instructions on how to open the package and use the product, so that patients have a clear understanding of how it works.

The manufacturing of oral films is a continuous but modular process that is suitable for automation. The modularity of the process, such as master

roll holds, allows for finished conversion to be done in the country or region of distribution, which complements satellite expansion based on regional demand. The manufacturing process has a low carbon footprint and a lower use of water for component preparation and sterilisation compared with other dosage forms.

PROMISING APPLICATIONS AND COMMERCIAL OPPORTUNITIES

Oral films are still a nascent dosage form and many exciting new applications and advances are being explored:

- The goal of replacing injection as the delivery route of choice for certain drugs, such as insulin, is one that oral film researchers and manufacturers are actively working towards.
- The combination of micro- and nano-drug encapsulation with oral films is a strategy being pursued to increase the bioavailability of certain drugs,⁴ such as those in the emerging field of cannabinoids.
- Higher loading of active ingredients in fast-dissolving films is being accomplished by using innovative multi-layer films. This opens the door for creating oral film formulations of lower potency drugs, such as antibiotics and antifungals.
- Films used for topical drug administration have the potential to greatly improve how oral sores are treated.

With respect to the popular concept of personalised therapy, oral films provide the unique ability to dispense an individualised dose of medication precisely, which is critical both for many paediatric drugs and drugs with narrow therapeutic indices that need to be carefully titrated. Oral films are the optimal dosage form to pair with innovative precision dosing software, such as BestDose.⁵ Lastly, the establishment of printing technologies for oral films could enable individually customised products, including fixed-dose combinations and very low doses.

In summary, the possibilities for this truly multi-faceted dosage form have only started to be realised.

ABOUT THE COMPANY

CURE Pharmaceutical is a vertically integrated drug delivery and development company committed to improving drug

efficacy, safety and the patient experience through its proprietary dosage forms and delivery systems. CURE has a full-service cGMP manufacturing facility and is a pioneering developer and manufacturer of a patented and proprietary delivery system (CUREfilm™), one of the most advanced oral thin film on the market today. CURE is developing an array of products in cutting-edge delivery platforms and partners with biotech and pharmaceutical companies. CURE has positioned itself to advance numerous therapeutic categories, including the pharmaceutical cannabis sector with partnerships in the US, Canada, Israel and Germany, among other markets.

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ABOUT THE AUTHORS

Rob Davidson is CURE's Chairman and Chief Executive Officer. Prior to his role at CURE Pharmaceutical, Mr Davidson served as President and Chief Executive Officer of InnoZen Inc, Chief Executive Officer of Gel Tech LLC, Chief Executive Officer of Bio Delivery Technologies Inc, and has served on multiple corporate boards. Mr Davidson has been responsible for the development of several drug delivery technologies and commercial brand extensions. He has a Masters Certificate in Applied Project Management from Villanova University, Masters of Public Health from American Military University, Virginia and a Masters in Health and Wellness from Liberty University, Virginia. Davidson also completed his postgraduate studies at the University of Cambridge (UK) with letter of commendation.

Jessica Rousset is CURE's Chief Operating Officer. Mrs Rousset oversees operations and drives corporate strategy and growth. She previously served as Head of Innovation at Children's Hospital Los Angeles, where over a ten-year period, she helped launch both therapeutic and medical device companies and founded and operated a national paediatric technology accelerator. Prior to that, Mrs Rousset held positions at the Scripps Research Institute and GlaxoSmithkline Biologicals in laboratory, clinical research and business development roles. She trained as a biochemical engineer at the Institut National des Sciences Appliquées in Lyon, France.

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ORAL DRUG RECONSTITUTION: MAKING IT EASY AND ACCURATE VIA PACKAGING INNOVATION

In this article, Anna Malori, PhD, Business Development Manager, Bormioli Pharma, discusses the oft overlooked challenges and difficulties of standard packaging systems for oral medications requiring reconstitution before use. Following on from this she highlights dual-chamber systems as a potential solution to this problem, with reference to a case study from Bormioli Pharma's own experience.

THE POTENTIAL RISKS UNDERLYING RECONSTITUTION

Every year, more than 900 million units of drugs are sold worldwide in a “to be reconstituted” state, with a corresponding value of about US\$3.0 billion (£2.25 billion).¹ Among these, orally administered drugs are the most common. But what does reconstitution really imply and how is it carried out normally? With standard reconstitution, a powdered drug is packaged in a glass or plastic bottle and the patient has to add the solvent themselves. The solvent – often water, but occasionally another liquid

– can be provided by the pharmaceutical company in a separate container or may not be provided at all. If solvent is not provided, the solvent choice and dosing are left in the hands of patient.

Let's try to imagine how a standard reconstitution process takes place when solvent is not provided. After receiving the medicine, the patient goes home and opens the drug package. At this stage, it is possible to run into one of two different kinds of packaging configurations:

- The first one is a bottle with a level mark, accompanied by an instruction leaflet. This is the case of a glass or plastic bottle containing the powder: the patient has to add water up to the level mark by following the instructions, mix and consume.
- The second one is quite similar but does not include the level mark on the bottle. In this case, the patient has to check the correct quantity of solvent in the instruction leaflet, autonomously dose it and add it to the bottle. The rest of the procedure does not change.

In both cases, human error is a significant concern. An untrained patient

"An untrained patient often undervalues the importance of some critical elements for drug reconstitution, such as the quality and the correct dosage of the water used during the procedure."



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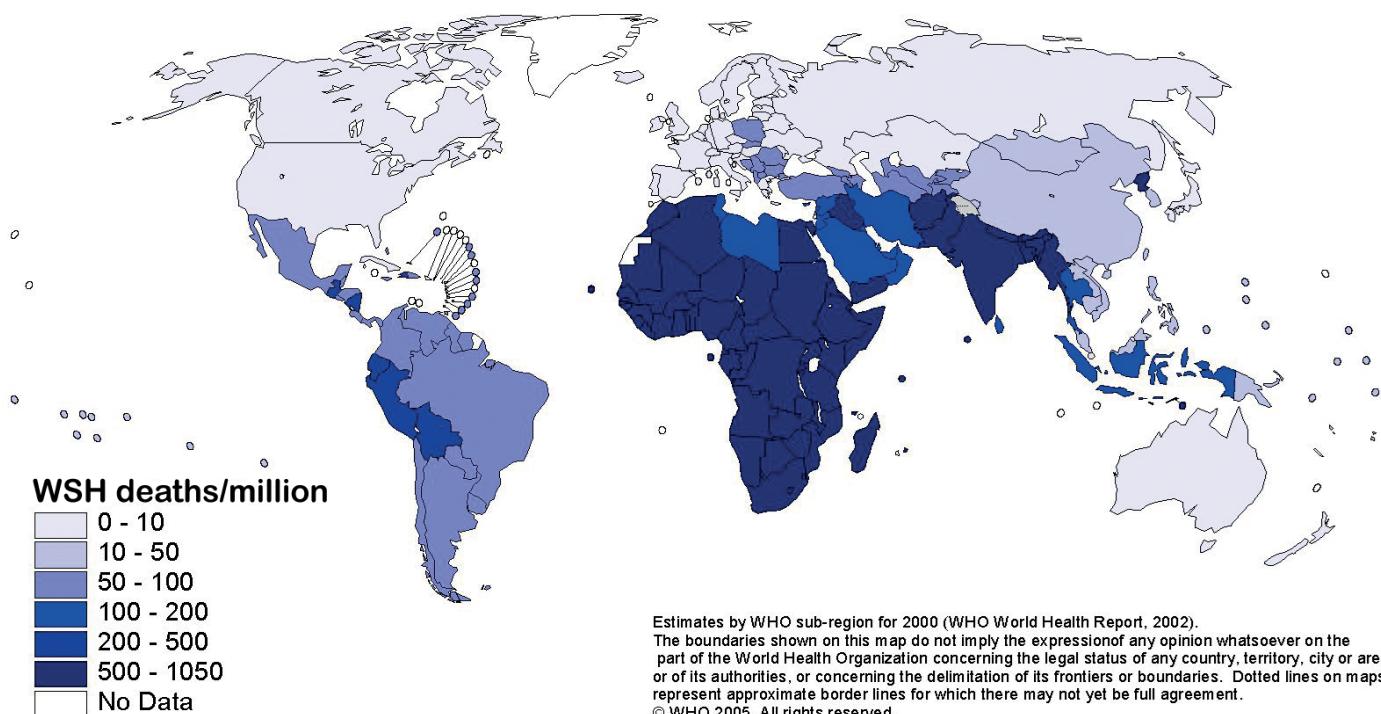


Figure 1: Map of deaths from unsafe water, sanitation and hygiene elaborated from World Health Organization (2005).

often undervalues the importance of some critical elements for drug reconstitution, such as the quality and the correct dosage of the water used during the procedure.

When discussing reconstitution, water quality is not a simple issue. An article from the American University of Sharjah (UAE) underlines all the possible concerns about the use of the wrong type of water while reconstituting.² First of all, it is uncommon for patients to be aware that, depending on the particular pharmaceutical process at play, a different type of water is required (e.g. purified or highly purified, mineral, spring, drinking, distilled) and that the wrong type of water can negatively impact on the drug's effectiveness. Secondly, patients often use tap water which may contain contaminants that exceed specific limits and as a result may lead to health problems.

This consideration is all the more true for those countries dealing with water pollution. A study conducted by the

WHO (Figure 1) shows that deaths due to unsafe water are a daily issue in many countries.³ For example, across almost the entire African continent there are anywhere from 550 to 1050 deaths per million inhabitants each year. It is clear that, in such countries, using tap water for reconstitution is not inappropriate, but actively dangerous.

Another potential error that can occur when reconstituting oral drugs is making a mistake in dosage. This could be either accidental or voluntary. Accidental mistakes happen when the patient does not use the prescribed dosage of water or powder, due to distraction or the poor level of accuracy of the measuring device (e.g. poorly designed or manufactured graduation



Figure 2: An example of a dual-chamber system with main features highlighted.

"A dual-chamber system leaves no dosing choice to the patient, as both the powder and the solvent are pre-dosed, ensuring a precise and accurate reconstitution and avoiding any occurrence of human error."

marks on cups and spoons). Voluntary mistakes are primarily caused by incorrect assumptions or fundamental misunderstandings of the product. For example, some people add more water than the stated quantity because they erroneously believe that this will allow them to have a greater quantity of the drug, thereby saving money.

It is important to note that both using either an excess or insufficient amount of water negatively impacts on the efficacy of the reconstituted drug. On the one hand, the direct consequence of adding too much water is a disproportionate dilution of the active ingredients, resulting in a loss of effectiveness. On the other hand, using not enough water can lead to serious problems of toxicity, as the active ingredients remain too concentrated.

INNOVATIVE PACKAGING SYSTEMS CAN BE AN ANSWER

As a pharma packaging manufacturer, Bormioli Pharma is well positioned to understand and tackle the challenges presented by reconstitution – namely complexity, dosage errors and poor safety features – by the design of novel packaging solutions. Specifically, this refers to the design of dual chamber systems (Figure 2) that allow for the reconstitution of oral drug product directly in the packaging itself, simply by following a guided procedure. A dual-chamber system is normally composed of a plastic bottle pre-storing the solvent and a cap pre-storing the powder. When the packaging is closed both the solvent and the powder are unavailable to the patient, who has no possibility of tampering with the pre-stored doses. The integrity of the packaging is ensured by a tamper-evident ring, which must be removed to make the reconstitution possible. After removing the tamper-evident ring, the patient

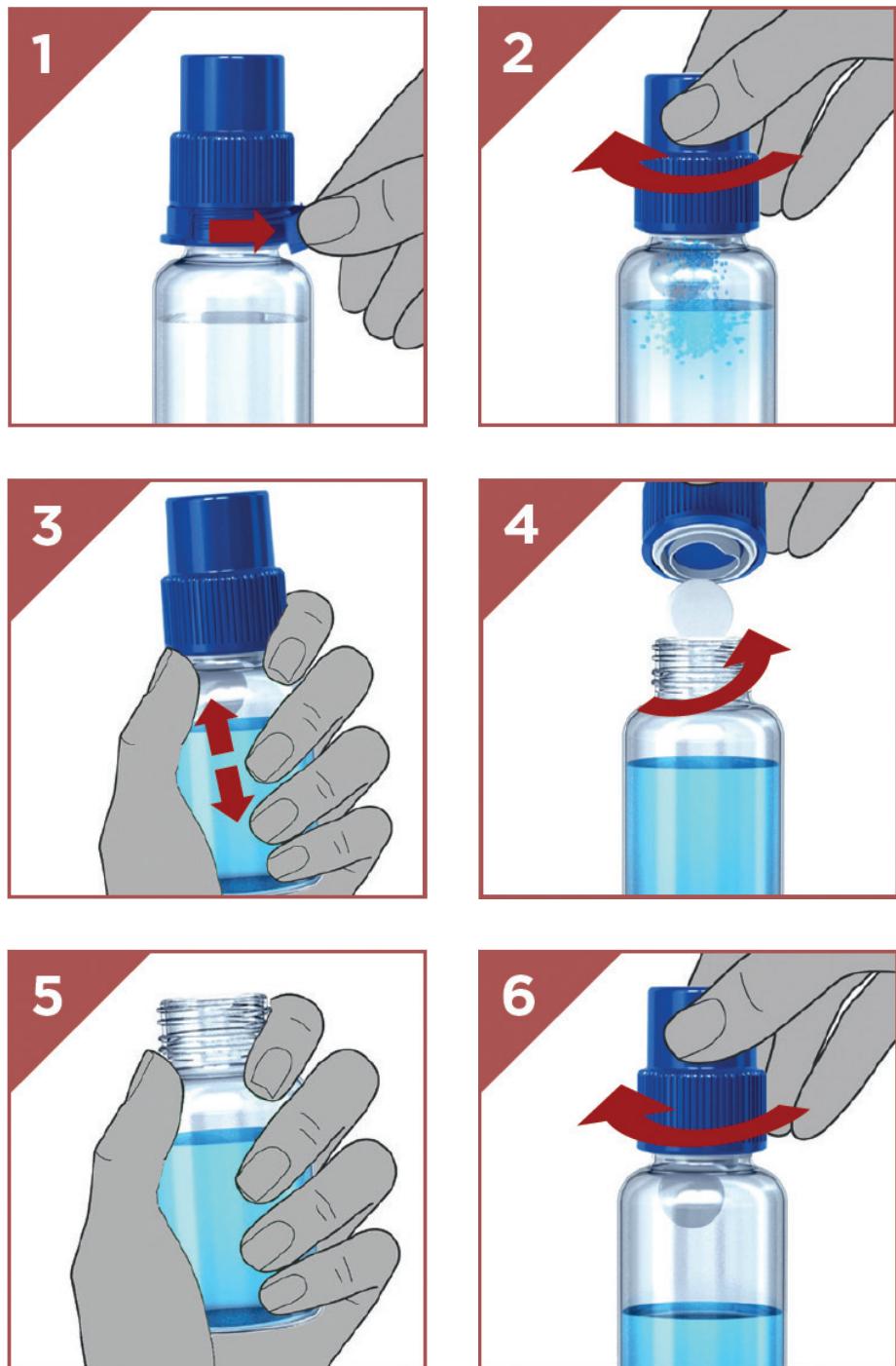


Figure 3: Functioning of a dual-chamber system in six steps.

only has to screw down the cap. This way, the powder falls down into the solvent and then the drug reconstitution procedure can be safely and accurately completed by shaking the bottle (Figure 3).

At this point, the advantages resulting from such a system should be self-evident. Firstly, a dual-chamber system leaves no dosing choice to the patient, as both the powder and the solvent are pre-dosed, ensuring a precise and accurate reconstitution and avoiding any occurrence of human error. Secondly, the solvent

is chosen and provided directly by the pharmaceutical company. According to research conducted by the American University of Sharjah,² providing pre-packaged water with all oral formulations that require water for reconstitution is the best way to avoid any confusion and health issues. Furthermore, the pharmaceutical company is free to choose what solvent to provide inside the packaging, allowing greater flexibility in drug formulation, since it will not be tied to water as a solvent anymore.

Alongside these advantages, dual-chamber systems offer other remarkable benefits in terms of drug protection. In contrast with standard packaging formats for drugs requiring reconstitution, dual-chamber systems offer no possibility for powder loss. This is because the powder is safely stored and sealed inside the packaging and thus well protected from when it is introduced into the primary packaging through to eventual use by the patient.

Case Study of a Dual-Chamber System

To better understand the potential of dual-chamber systems with respect to improving oral drug reconstitution worldwide, a practical case can be useful. Bormioli Pharma as a primary packaging manufacturer for the pharmaceutical and biopharmaceutical industry has worked with one of the world's leading pharmaceutical companies. Bormioli Pharma was first contacted by this customer when it was dealing with a serious issue regarding one of its best-selling paediatric antibiotics, sold as powder packaged in a glass bottle with a level mark. Patients needed to add water into the bottle up to the level mark in order to reconstitute the product. But there were two problems:

1. The country where the antibiotic was sold had extremely poor water quality.
2. People were not trained to reconstitute antibiotics and they erroneously believed that the more water they added, the greater quantity of product they obtained.

Repackaging was seen as a possible solution to avoid these problems. Changing the dosage form, for example shifting from a reconstitutable powder to a solid tablet, however, was not taken into consideration because pills are difficult to

swallow for children.

Together with Bormioli Pharma, the customer decided to adopt a dual-chamber system to improve the safety and the effectiveness of the medication. The first dual-chamber system prototypes were presented to the customer and a joint focus group was organised to evaluate both the ease of use and functionality of the product. From the very beginning, it was seen as an advantageous change. Indeed, Bormioli Pharma's solution would have solved their issues but wouldn't have required any drug product reformulation. Only the filling and dosing processes had to be adapted to the new packaging configuration.

The development process encompassed several phases and continuous bilateral meetings alongside the customer to ensure an optimal final packaging configuration. The result was a paediatric antibiotic, safely packed in a dual-chamber system to ensure water quality and dosing precision. In addition, simple figurative instructions were printed directly on the packaging to enhance patient compliance and to improve the correct use of the product.

SUMMARY

As has been discussed, oral drugs to be reconstituted – antibiotics, syrups or high-value treatments – represent an important segment of the global pharma industry. However, the standard reconstitution process still seems to be too complex, not completely safe, and subject to different types of human errors. Packaging manufacturers and pharmaceutical companies can work together in order to develop effective solutions to make reconstitution more precise, safer and easier. Amongst the potential solutions, dual-chamber systems

appear to be a strong alternative to standard packaging methods.

ABOUT THE COMPANY

Bormioli Pharma is a primary glass and plastic packaging manufacturer serving the pharmaceutical, biopharmaceutical and nutraceutical markets. With more than 40 years' experience in the dual-chamber systems segment, Bormioli Pharma was one of the first packaging suppliers in the world to develop the bi-phase technology.

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ABOUT THE AUTHOR

Anna Malori, PhD, received a Chemistry and Packaging Technology degree from the University of Parma, Italy. As Business Development Manager at Bormioli Pharma, she works to detect unmet market needs from which to develop new business opportunities. Dr Malori is responsible for product pipeline management, leading her to collaborate closely with the R&D team.



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EXCIPIENT INNOVATION REQUIRES CLOSE COLLABORATION BETWEEN SUPPLIERS AND DRUG FORMULATORS

Here, Michael Baumann, PhD, Pharma Field Marketing Manager EMEA, Dow Pharma Solutions, discusses the need for novel excipients in new drug development, the regulatory difficulties inherent to developing novel excipients and methods of innovation using current compendial excipients.

Close working relationships between drug manufacturers and excipient suppliers with a deep understanding of the composition, functionality and performance of excipients in drug formulations have never been more important. For starters, excipients are no longer considered inactive, and thus have become a top priority among regulatory bodies worldwide. Regulatory agencies in the US, EU, Japan and the BRICK countries – Brazil, Russia, India, China and Korea – are placing more focus on excipient regulations and guidelines or introducing new rules for finished pharmaceutical products that specifically address excipients, directly or indirectly.

Whilst necessary, such regulations have a tendency to discourage innovation, particularly when it comes to the lack of a defined regulatory pathway to facilitate the approval of novel excipients. In fact, only three novel excipients have been launched and approved over the past 20 years, according to professor Brian Carlin, immediate past chair of the International Pharmaceutical Excipient Council (IPEC) of the Americas' Quality by Design (QbD) Committee, at the IPEC Europe Excipient Forum (Bordeaux, France, Feb 1 2018).

Recognising the need for a regulatory process to enable the evaluation and acceptance of novel excipients to support innovation in the pharmaceutical industry, IPEC-Americas has partnered with the International Consortium for Innovation and Quality of Pharmaceutical

"By some estimates, as many as 90% of new chemical entities fall into Class II and Class IV of the biopharmaceutics classification system."

Development (IQ) to collaborate with the US FDA in their Critical Path Innovation programme, according to Priscilla Zawislak, Chair IPEC-Americas.

INNOVATION DRIVERS

Beyond the regulatory landscape is an urgent need for collaborative excipient innovation. Excipients are indispensable ingredients in final drug formulations that can impact product quality, stability, tolerance, release profiles, overall efficacy and safety. They are also critical to efficient drug processability, ranging from direct compression and roller-compaction to hot-melt extrusion.

Perhaps most important of all is the issue of solubility, which has emerged as a major barrier to the formulation of bioavailable dosage forms. Pharmaceutical pipelines are dominated by low-solubility drug candidates. By some estimates, as many as 90%¹ of new chemical entities (NCEs) fall into Class II and Class IV of the biopharmaceutics classification system (BCS).



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There is an urgent need for excipients, processes and technologies that can overcome the inherent limitations of low-solubility NCEs. The importance of collaboration is, in part, a reflection of the scope and scale of the challenge posed by poorly-soluble NCEs. Inter-company and, particularly, interdisciplinary collaborations are needed.

THREE PRACTICAL EXCIPIENT INNOVATION PATHWAYS

There are at least three ways for drug formulators and excipient suppliers to work together to innovate within the compendial box:

1. Co-processed excipients (CPEs), which are a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change.²
2. Modified morphology, or physical properties, of compendial excipients within the allowed ranges of existing regulatory monographs.
3. Modified molecular structure of compendial excipients within the allowed ranges of existing regulatory monographs.

Methods two and three are, in effect, significant line extensions of existing compendial excipients. If a change of excipient morphology and/or molecular structure yields an excipient that still meets the compendial monographs, the tailored excipient would still fall within the IID excipient category.

Development of innovative excipients through any of these pathways does not create a novel chemical entity, but it does

"When drug formulators share their specific excipient challenges regarding APIs, formulation and/or processing, knowledgeable excipient suppliers can help determine the optimal innovation pathway."

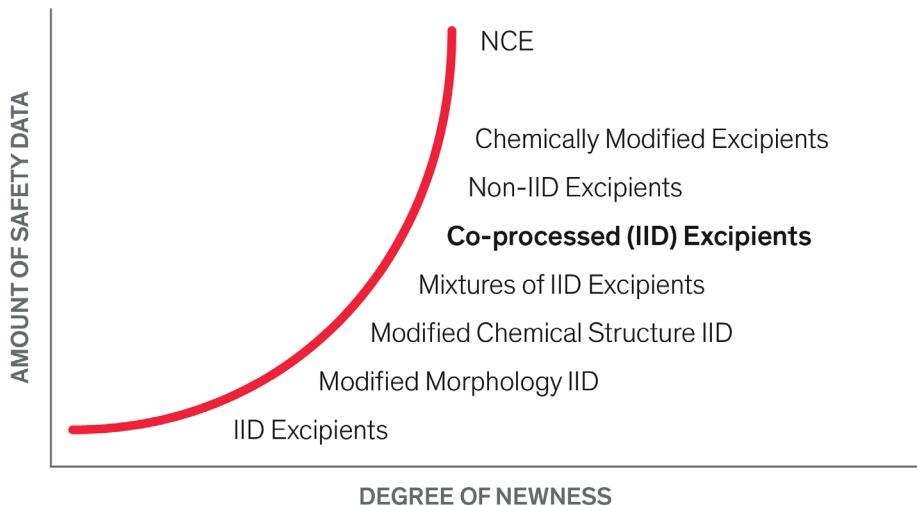


Figure 1: Excipient regulatory and environmental challenges.

create a novel regulatory entity. They may require regulatory review, but not nearly so rigorous as those required of a genuine NCE. In general, excipients developed by these three methods will need a thorough safety analysis and analytical proof that the "new" excipient retains the same chemical nature as the parent excipient. In the case of CPEs that combine two or more compendial excipients, if it is proven there is no covalent bond between the parent excipients, then safety of the co-processed excipient can be derived from a safety profile of the individual components (Figure 1).

When drug formulators share their specific excipient challenges regarding APIs, formulation and/or processing, knowledgeable excipient suppliers can help determine the optimal innovation pathway. For instance, Dow utilises a design of experiment (DOE) approach to explore substituent space and customise optimised, robust performance for poorly soluble drug compounds. This approach combines polymer structure-property relationships with small scale synthesis capability to address the unique needs of each API.

Here follows a brief review of these three excipient innovation pathways.

Co-Processed Excipients

Because they are typically comprised of two or more compendial excipients, the majority of new excipient developments are co-processed products. According to IPEC, the most popular CPEs today are designed to facilitate cost-saving direct-compression (DC) manufacturing processes. However, they are also engineered to address challenges such as limited solubility, permeability, improved flow, increased gel strength and better sensory attributes.

CPEs are developed to engineer a benefit beyond the simple blending of two or more excipients. They are created by incorporating one excipient into the particle structure of another in order to mask the undesired properties of some materials whilst retaining, or improving, desired properties of other materials, resulting in a targeted performance enhancement.

For instance, microcrystalline cellulose (MCC) – a pharmaceutical excipient dating back to 1962 – has excellent binding properties, but MCC shows plastic deformation during tabletting, resulting in increased lubricant sensitivity. This can slow down production speeds and lead to softer tablets. Incorporation of excipients such as dicalcium phosphate or

Co-Processed Ingredient	Advantages
Silicon dioxide	Improved flow, compatibility
Dicalcium phosphate	Improved compatibility, especially for dry granulation
Mannitol	Improved flow, decreased lubrication sensitivity
Guar gum	Improved sensory attributes in chewable tablets
Carboxymethylcellulose	Superior gel strength and thixotropic behavior in suspensions

Table 1: Recent MCC co-processed excipients.

silicon dioxide into the MCC particle structure minimises the effect of the lubricant on tablet strength and helps improve tabletability. Various grades of MCC have recently been improved through incorporation of other excipient materials (Table 1).

IPEC believes that the majority of new developments in the foreseeable future will involve co-processed excipients. However, with the exception of MCC/carboxymethylcellulose sodium, silicified MCC and compressible sugars (sucrose + maltodextrin) – CPEs are not yet listed in the monographs, whereas the other two approaches to excipient innovation, modified morphology and modified molecular structure, offer opportunities to improve performance entirely within existing pharmacopeias.

Modified Morphology Excipients

A second pathway for excipient innovation involves modification of particle shape, size, surface area and/or porosity. Accomplished within existing compendial parameters, this approach reduces the necessary regulatory approval significantly since the excipient material has not changed chemically.

As an example, hypromellose (hydroxypropyl methylcellulose, or HPMC) has long been used as a hydrophilic polymer excipient to create controlled-release matrix tablet formulations. However, its morphology may present problems to formulators trying to utilise a direct-compression process for tablet manufacture. A modified morphology of hypromellose is Dow's METHOCEL™ DC2 family of premium cellulose ethers, a line extension jointly developed with Colorcon (Dartford, UK) using Dow's patented designed particles morphology (DPM) technology.

For METHOCEL™ DC2, the powder morphology was optimised to increase flowability by reducing the concentration of fibrous particles that hinder powder flow, without either sacrificing other critical tablet and formulation properties or coprocessing it with any flow aids. Figure 2 compares the particle morphologies of METHOCEL™ CR (thin, flattened, elongated fibrous particles) with METHOCEL™ DC2 (tightly controlled, thicker, more rounded particles).

An internally developed funnel flow test was used to compare the powder flowability of neat METHOCEL™ DC2 and METHOCEL™ CR over a 14 second

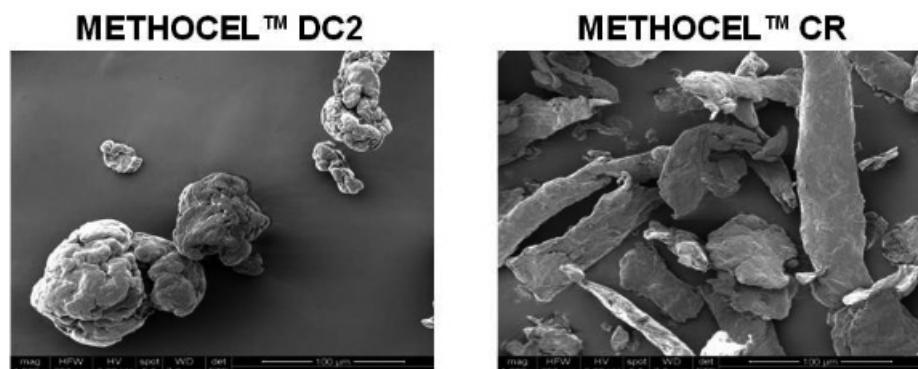


Figure 2: Comparison of particle morphologies.

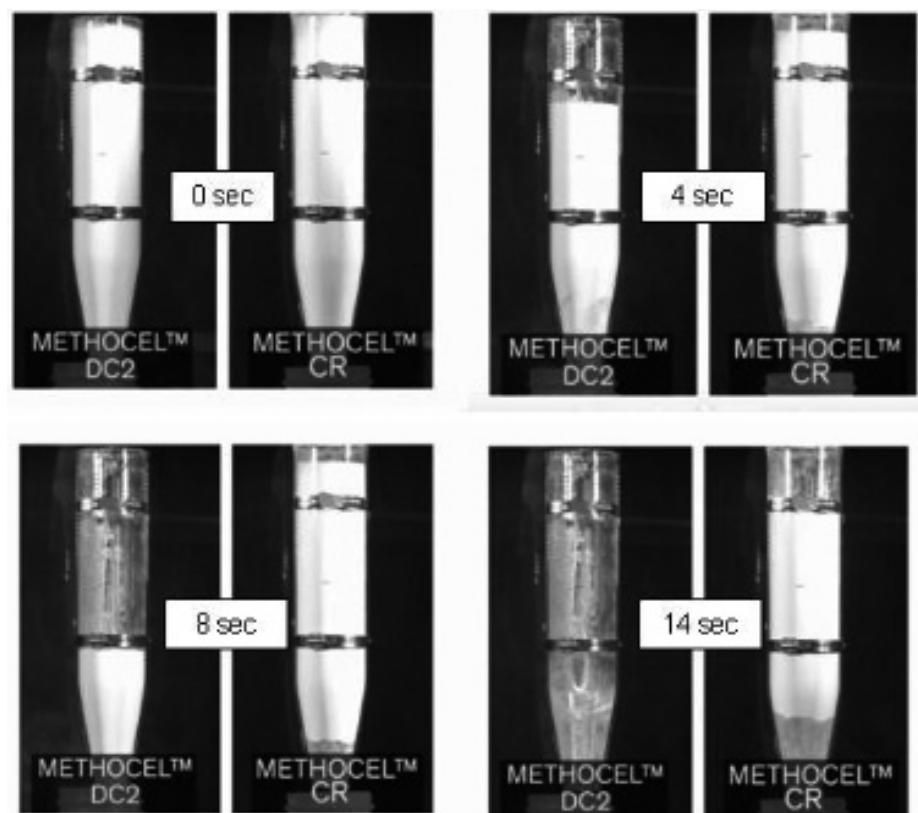


Figure 3: Comparison of METHOCEL DC2 and METHOCEL CR powder flow properties.

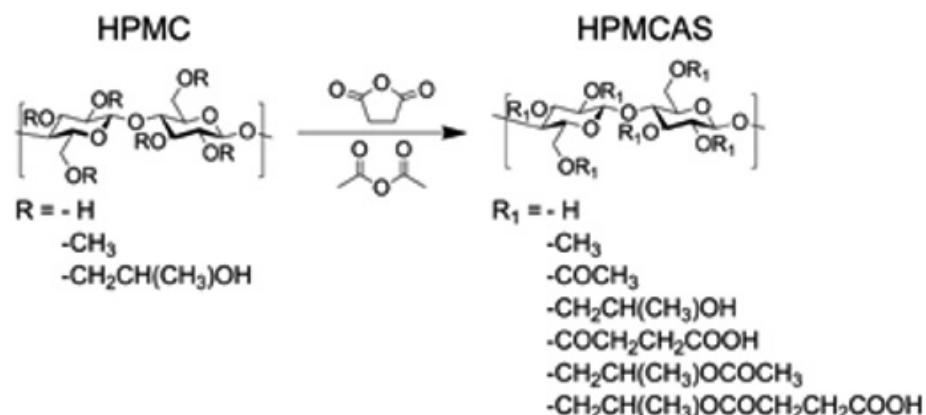
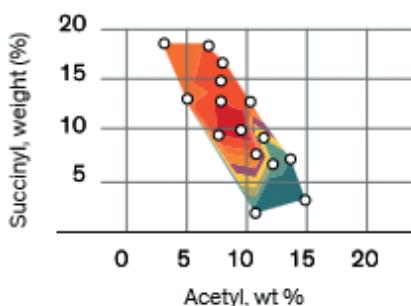
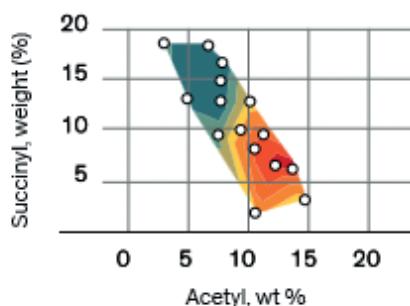


Figure 4: Reaction scheme to convert HPMC to HPMCAS.



ITZ AUC90

■ ≤ 8200	■ ≤ 4.37e+4
■ ≤ 1.53e+4	■ ≤ 5.08e+4
■ ≤ 2.24e+4	■ ≤ 5.79e+4
■ ≤ 2.95e+4	■ ≤ 6.5e+4
■ ≤ 3.66e+4	



GRIS AUC90

■ ≤ 1.4e+4	■ ≤ 2.6e+4
■ ≤ 1.7e+4	■ ≤ 2.9e+4
■ ≤ 2e+4	■ ≤ 3.2e+4
■ ≤ 2.3e+4	■ ≤ 3.5e+4

Figure 5: Performance maps: red is highest solubility; blue is lowest solubility; with the AFFINISOL™ HPMCAS quality-by-design sample set with model compounds itraconazole (ITZ) and griseofulvin (GRIS).

period (Figure 3). METHOCEL™ DC2 exhibited a more fluid-like behaviour, indicating that it can exit a hopper outlet more readily, travel through a feeder better and fill a tablet press die more evenly – attributes that facilitate direct-compression processing.

Widely used in the global pharmaceutical industry today, the METHOCEL™ DC2 line of cellulose ethers demonstrates the efficacy of the designed morphology approach for excipient innovation; in this case enabling a switch from batch wet granulation to continuous dry processing. The entire line of METHOCEL™ cellulose ethers, including METHOCEL™ DC2, complies with the current US, European and Japanese Pharmacopeias.

Modified Molecular Structure

If formulators are willing to share sufficient information regarding an API's chemical structure and intended purpose, an experienced excipient supplier can modify the structural molecular properties of their excipients and tailor the molecular properties to make them more suitable to a particular API – without changing the fundamental chemistry and within existing compendial parameters.

An example of this approach is Dow's AFFINISOL™ hypromellose acetate succinate (HPMCAS), offered to help formulators to overcome solubility issues of poorly soluble APIs by formulating stable amorphous solid dispersions (e.g. via spray-drying processes). AFFINISOL™ HPMCAS

is an HPMC material functionalised with a mixture of monosuccinic acid and acetic acid esters (Figure 4).

This modified molecular product helps not only to formulate stable amorphous dispersions, but also inhibits API crystallisation in solution, promoting supersaturation of the drug. A key attribute of AFFINISOL™ HPMCAS is its flexibility in acetate and succinate substitution levels. This allows tailoring of the molecular structure of this excipient within the compendial ranges to the specific needs of the API, which results in optimised solubility enhancement and material processing. The performance maps in Figure 5 demonstrate the need to have a full understanding of the allowable HPMCAS substitution space and how minor changes in acetate and succinate substitution can have a substantial impact on solubility enhancement.

These combined properties make AFFINISOL™ HPMCAS an excellent choice for formulating BCS Class II and Class IV compounds. It is also a prime example of excipient innovation by modifying the molecular structure of excipients already approved in the existing pharmacopeias.

NOVEL EXCIPIENT CHALLENGES

Lack of an official FDA approval process for new excipients independent of finished drug formulations has hindered excipient innovation, but this should not stop innovation outside the compendial box.

Novel excipients offer unique technical benefits and untapped potential for solving a host of challenges.

A case in point is Dow's AFFINISOL™ HPMC hot-melt extrusion (HME) excipient, an HPMC material designed with a polymer substitution architecture that enables thermal processability in HME processes. This novel excipient offers extended HME process flexibility for choosing polymer viscosities that optimise solubility and drug release profiles, among many other benefits.

The path to approval for AFFINISOL™ HPMC HME may be long, but the benefits are worth it. Dow Pharma Solutions is raising awareness of the benefits and safety of novel excipients by hosting global seminars and working with the FDA to refine its approval process.

Hopefully, there will also be greater collaboration between pharmaceutical and excipient manufacturers in the development of new excipients. Open communication will lead to significant advances in excipient technology, enhancing drug development and allowing more patients greater access to better medicines.

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Michael Baumann studied chemistry at the Clausthal University of Technology (Germany) and holds a doctorate from the Institute for Technical Chemistry. He started his career at the Dow Chemical Company as an R&D leader in 2001 exploring and advancing polymer development for various industrial and pharmaceutical applications. In 2015, Dr Baumann took on his current role as the Pharma Field Marketing Manager, EMEA, for Dow Pharma Solutions.

THE SCIENCE OF SOLUBILITY AND THE SUCCESS OF AMORPHOUS SOLID DISPERSIONS

In this article, Rashmi Nair, Senior Scientist, Formulation R&D, Dr Reddy's Laboratories, discusses the persistent challenge presented by poorly soluble drug formulations in oral drug delivery. Furthermore, she goes on to highlight the promise shown by amorphous solid dispersions, despite the difficulties they present.

INTRODUCTION

Oral drug delivery is generally considered to be the most common route of drug administration, due in large part to the fact that it offers major advantages, such as self-administration, non-invasiveness and cost-effective

production. Oral delivery constitutes about half of the total drug dosage forms in use today. In 2017, the US FDA approved 46 drugs, of which 24 were oral dosage forms.¹

As a drug traverses the gut, it encounters various environments, enzymes, pH media, microflora, etc. The drug dissolves, solubilises and then permeates through cellular membranes to impart its action. This seemingly simple process is jeopardised when a drug undergoes first-pass metabolism, does not dissolve or has permeability issues, and such cases are not rare. About 17% of clinical attrition is attributed to pharmacokinetic and bioavailability issues.²

The biopharmaceutical classification system (BCS) was introduced in 1995 and continues to be a reference for preliminary evaluation and categorisation of drugs as soluble, permeable or otherwise. *In vitro* and *in silico* tools have added advanced predictability to the drug discovery and development process.³ Yet still the challenge of poorly soluble drugs with bioavailability issues remains under resolved.

One major reason attributable here is the way in which drug development is currently happening. The focus of lead selection and optimisation is to show pharmacological activity at target sites/receptors (biological selectivity and specificity). For this, lipophilic ligands are added to drug structures, which in turn generate highly lipophilic drugs that present challenges of solubility in biological fluids. This problem is usually only identified in late clinical

"Ideally, a holistic plan to evaluate and address bioavailability challenges should be devised at the initial drug development stage."

stages, while during preclinical *in vivo* and *in silico* testing the early formulations are either solutions in solvents, surfactants, etc, or the issue is masked by a low drug dose.⁴ To a large extent, enabling formulation interventions can address solubility and bioavailability challenges of drugs.⁵ Time to evaluate the need for such interventions is critical.

Ideally, a holistic plan to evaluate and address bioavailability challenges should be devised at the initial drug development stage. It is easier to make process changes when the product is in the drug substance development stage than in the drug product. Two examples of processes which could potentially benefit the drug development process are the use of crystallisation models for small size crystals, which could avoid micronisation, or the evaluation of various solid forms, which could help select more soluble forms, such as an amorphous form. "Formulate-ability" can be better assessed if an integrated approach is followed from drug discovery to drug product development.⁶

THE SCIENCE OF SOLUBILITY

A combination of prognostic and diagnostic tools would be required for assessing the solubility and bioavailability challenges of a drug. One of the first steps is to determine solubility. It is important that the solubility testing is performed in the relevant media, representing the physiological environment that a drug is likely to encounter *in vivo*. Intrinsic dissolution testing, pH solubility



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profile and solubility in simulated fluids (gastric, intestinal, etc) can provide valuable information as to whether a drug has a solubility and/or bioavailability challenge and, if so, what the cause may be.

The possible causes include solvation-limited solubility (grease ball drugs that have high log P/log D values, i.e. >3) and solid state-limited solubility (brick dust drugs that have a high melting point, i.e. >200°C), both of which need to be addressed with enabling formulation strategies.⁷ Few drugs have characteristics of both classes, i.e. high log P values and high melting point like levothyroxine (log P 4.6 and T_m 235°C) and are therefore difficult to formulate.⁸ Increasingly the role of *in silico* tools, *in vitro* tests and computational predictions have to play being recognised.⁹

Bioavailability is an important pharmacokinetic parameter that defines the fraction of drug reaching systemic circulation. Various factors, physiological and physicochemical, affect bioavailability. When devising a strategy for enhancing bioavailability, it is important to identify the reason bioavailability is low in the first place.¹⁰ Formulation interventions are better suited to situations where bioavailability is a function of drug's dissolution and solubility. Permeability

modulations, though possible, are not very easy to achieve because of the multiple factors that exert influence in this area.

FORMULATION INTERVENTIONS FOR SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

As per the BCS, class II and class IV drugs are amenable to formulation interventions for solubility and bioavailability enhancement (Figure 1).¹¹ Selection of appropriate formulation strategy would depend on following considerations:

- Stage of drug development where formulation is required:** At the early stages of drug development (preclinical and before), availability of limited drug quantities and constraint of time and money necessitate that a simple, reproducible and physico-chemically stable formulation is developed. From Phase I onwards, a more in-depth study is possible and various formulation strategies could be evaluated. However, if a solubility enhancement is applied at later stages, it calls for a bridging study between the early- and late-phase formulations,¹² which would obviously result in additional work and cost.

"Any enabling formulation approach needs to distinguish itself as discovery formulation, preclinical formulation or clinical formulation. Until late-stage clinical study, it is preferable to keep the formulation as simple as possible..."

- Purpose of formulation:** It is important to understand the purpose of a formulation development, e.g. a toxicology study requires the maximum exposure of a drug, a Phase I study is for dose ranging, Phase II requires a composition that is closer to the market product, etc. Each phase has clear objectives and a fit-for-purpose formulation should be designed. Accordingly, the approach that is utilised for enabling formulation development needs to be considered.

It would be appropriate at this juncture to state that any enabling formulation approach needs to distinguish itself as discovery formulation,¹³ preclinical formulation¹⁴ or clinical formulation.¹⁵ Until late-stage clinical study, it is preferable to keep the formulation as simple as possible, mainly for the following reasons:

- Addition of many additives/excipients would require extensive drug excipient compatibility studies.
- Complex technologies would require a lot of work on the process, its optimisation, scale-up, etc. This would delay the drug to dosing stage.
- Until Phase I/IIa, formulation development is an iterative process which could involve various changes to the target *in vivo* profile of the drug. Therefore, investing in sophisticated product design/process would not be appropriate.

There are various tools that are utilised to support the decision of which enabling formulation approach should be selected for a poorly water-soluble drug.¹⁷ Formulation scientists are moving towards a more

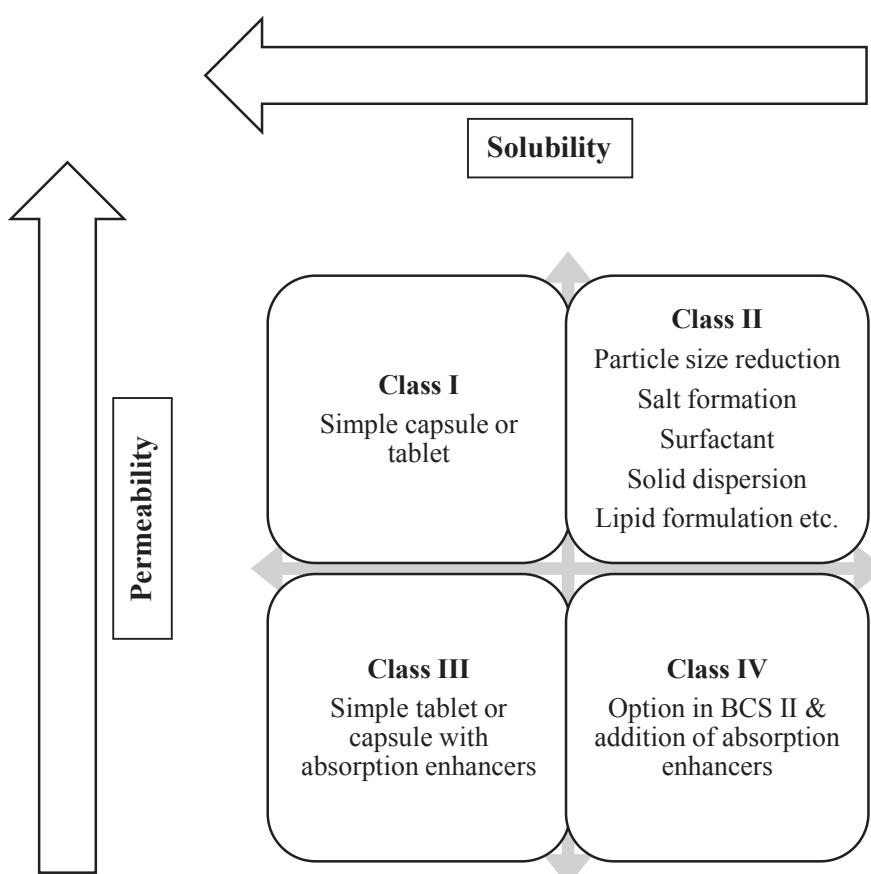


Figure 1: The BCS system of drug classification.

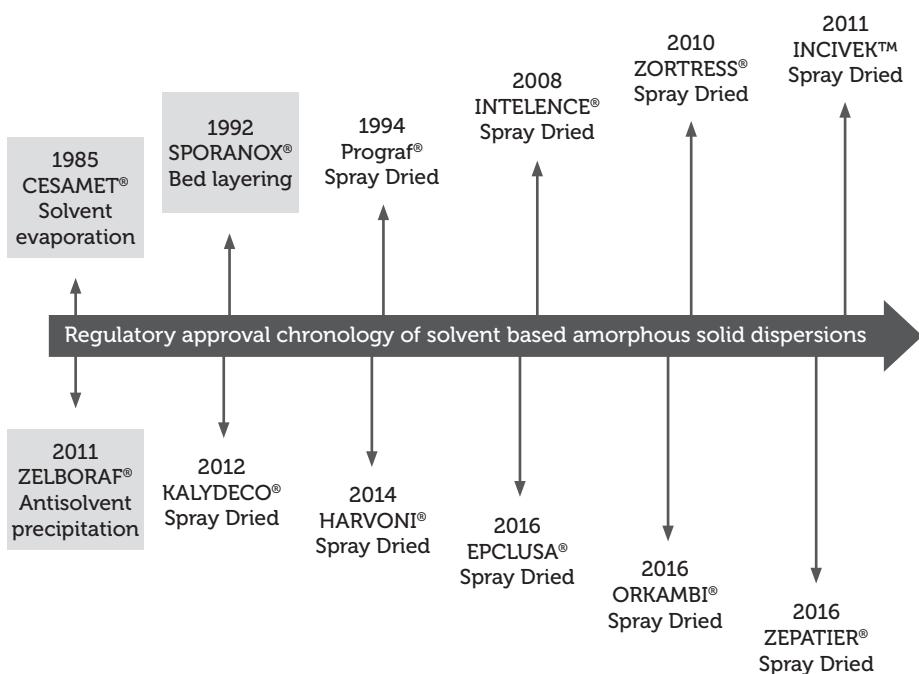


Figure 2: Chronology of product approvals for solvent-based ASDs.

"In recent years there has been a surge in the utilisation of amorphous solid dispersion technology.

In spite of the challenges of solid state stability, it is continuing to garner the attention of researchers..."

structured and predictive model. A few important tools are:

- High throughput screening (HTS) of physicochemical and biological properties
- Mini-scale preparation, *in vitro* testing and *ex vivo* studies
- Guidance maps
- Decision trees
- Computer modelling and simulations.

Drug classification systems are also evolving from the BCS to the developability classification system (DCS). The DCS was devised by Butler and Dressman¹⁸ and it subdivides class 2 into 2a (dissolution rate limited) and 2b (solubility limited), further guiding the decisions for appropriate enabling formulations.

Thoroughly knowing the drug molecule is the best way to identify and resolve solubility and bioavailability challenge.

AMORPHOUS SOLID DISPERSIONS

In recent years there has been a surge in the utilisation of amorphous solid dispersion (ASD) technology. In spite of the challenges of solid state stability, it is continuing to garner the attention of researchers, a fact which is evident from the success of products that are majorly produced by solvent-based methods (Figure 2) or using hot melt extrusion (Figure 3).

An interesting point to note here is that a lot of research is directed towards certain particular areas which are process oriented (Figure 4), using ASDs as an intervention to the challenge of poor drug solubility and bioavailability. Particularly, hot melt extrusion is drawing lot of attention considering its ability to offer continuous manufacturing and in-line analysis.

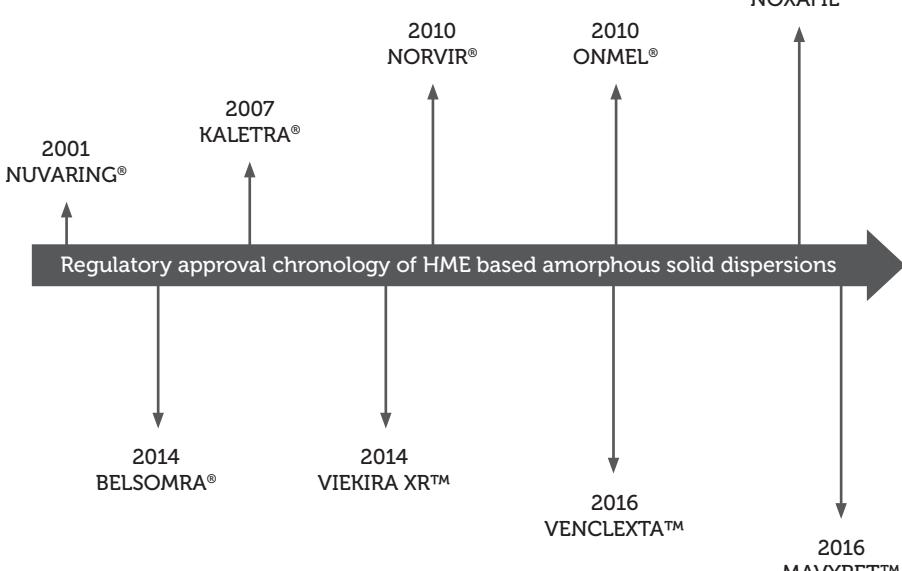


Figure 3: Chronology of product approvals for hot melt extrusion-based ASDs.

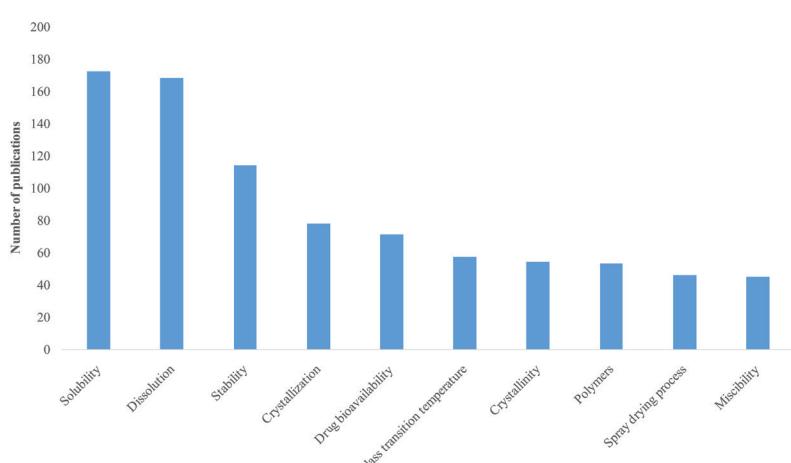


Figure 4: Top ten areas of research in ASDs.

Parameter	Analytical Method	Test Information
Preliminary Screening		
Glass forming ability (GFA)	DSC	Glass transition temp. (T_g)
		Onset temp. of crystallisation (T_{cr})
		Onset temp. of melting (T_m)
		Enthalpy of melt ΔH
Thermal stability	TGA/DSC	Decomposition temperature
Solid state	PLM	Amorphous/crystalline
	XRD	
Moisture sorption	DVS	Moisture sorption
Stability in aqueous pH solutions	HPLC/UV/HSM	Assay
Stability in organic solvents/co-solvents		Related substances/stability
Miscibility in polymers		
Dissolution in simulated media	HPLC/UV	Assay
		Related substances/stability
Stability (shelf life)	Mouthfeel	A drying, puckering and shrinking sensation in the oral cavity causing contraction of body tissues.
Advanced Characterisation		
Thermodynamics of drug-polymer interaction	FTIR	Chemical mapping
Relative interactions of prototypes	FTIR/NMR/Raman	Spectral imaging

Table 1: Typical analytical testing parameters and methods for ASDs.

From laboratory-scale screening to clinical and commercial production, this approach requires a sound understanding of factors such as chemistry, polymer science, analytical characterisation and engineering. Also, the characterisation requirements (Table 1) require a deep scientific understanding. Therefore, integrated organisations that have the necessary capabilities for development, manufacturing and analytical characterisations in-house are well suited to take on such products.

CONCLUSION

Most technology-based products add some complexity in development but have the potential to provide enormous benefits in terms of product intellectual property

and limited competition. It is worthwhile to assess and utilise technologies like ASDs, which could be used as early as the preclinical phase and eventually transform into commercial products. Regulatory authorities are encouraging well-controlled, process-based products through initiatives supporting continuous manufacturing and application of process analytical technology (PAT) tools.

In the next few years, amorphous solid dispersion technology is likely to see greater technical advancements.

The views and opinions expressed in this article are solely those of the author and are not necessarily shared by Dr Reddy's Laboratories or any other organisations with which the author is affiliated.

ABOUT THE COMPANY

Dr Reddy's Laboratories Ltd is an integrated pharmaceutical company, committed to providing affordable and innovative medicines for healthier lives. Through its three businesses – Pharmaceutical Services & Active Ingredients, Global Generics, and Proprietary Products – Dr Reddy's offers a portfolio of products and services including APIs, custom pharmaceutical services, generics, biosimilars and differentiated formulations. The company's major therapeutic areas of focus are gastrointestinal, cardiovascular, diabetes, oncology, pain management and dermatology. Dr Reddy's operates in markets across the globe, including the US, India, Russia & CIS countries and Europe.

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Rashmi Nair is Senior Scientist (Pharmaceutical Product Development) at Dr Reddy's Laboratories Ltd. She is a qualified pharmaceutical professional with supplementary roles of lead technical associate to business and certified in intellectual property/patents.

In the last decade of her work at the Custom Pharmaceutical Services (CPS) division of Dr Reddy's, she and her team have worked with various innovator companies from the US, Europe and Asia Pacific for development of proprietary technologies and have specialised in bioavailability enhancement techniques for new chemical entities and repurposed drugs in clinical studies.

The focus of her work, as reflected in her international papers and presentations, has been to highlight importance of simplified innovation and integrated development between chemistry, pre-formulation, formulation and manufacturing teams.

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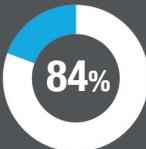
Senior Manager, Akums drugs and Pharmaceuticals

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