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Introduction

Optimising Drug Delivery: The Challenges and Opportunities

By Patrick Crowley and Luigi Martini

Most medications are taken orally and provide a bolus of drug for rapid absorption. Such delivery may be satisfactory in many cases. However, absorption and distribution usually delivers drug to many tissues, organs and cells as well as to the site of activity. Such widespread presence may cause unwanted effects. Additionally, onset and duration of action may be sub-optimal.

Better information during the early stages of drug development should lead to better dosage form design and better medications. However, it has usually been impossible to generate much meaningful knowledge before efficacy and safety is established. Furthermore, not every drug is amenable to enhancement by formulation even when there is good clinical rationale for doing so.

It is important therefore to be aware of the opportunities and the limitations for designing and administering formulations that are better targeted or otherwise controlled. Current approaches, initially in oral drug delivery but also in other delivery routes, are discussed in this review. Perspectives are also presented on future possibilities for novel ways of drug delivery to optimise efficacy and reduce unwanted effects.

Optimising Drug Delivery/Targeting

The ideal medication provides the requisite amount of drug at the site of its biological action and sustains its effect for a suitable time. Requirements may be dictated by the clinical condition, the mode and dynamics of the drug’s action and patient-related considerations such as age, health, genetic makeup and presence of other clinical conditions.

Drug delivery from the dosage form should ideally take account of such considerations. Historically, such dosage form design, particularly for novel structures, was constrained by lack of or limited information for optimising performance. Clinical assessment programs may have utilised dose frequencies that were based on the pharmacokinetics of the drug, with doses reflecting what was tolerated in Phase I volunteer trials. Material was usually dosed orally to optimise patient convenience and compliance. Many potentially useful materials may have failed to demonstrate safety and efficacy because of such modes of evaluation. Compound attrition was high.

This situation is changing. New insights concerning drug-receptor relationships, better diagnostic techniques to monitor performance, technologies for improved delivery, along with advances in molecular biology, genomics and other sciences are providing opportunities for better dosage form design and better medications.

“New insights concerning drug-receptor relationships, better diagnostic techniques to monitor performance, technologies for improved delivery, along with advances in molecular biology, genomics and other sciences are providing opportunities for better dosage form design and better medications”

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(repurposing) existing drugs to improve performance in approved conditions or use in other therapeutic areas.

**DRUG DELIVERY: ORAL DOSAGE**

Oral dosage is likely to remain the most popular mode of drug delivery route for a number of reasons. It is important then to be aware of the factors that might impede his mode of dosage:

- It may not be possible to provide, and sustain optimum or consistent drug levels at the intended target (site of activity)
- Time of arrival at the target (and associated onset of action) may not be optimal.
- Drug delivered to compartments other than site of action may evoince undesirable effects.

**THE GASTROINTESTINAL TRACT**

A drug dosed orally can encounter several barriers, while en route to systemic compartments. It may be inactivated by low pH in the stomach or by digestive enzymes in the intestinal lumen. Designing a dosage unit to obviate such attrition may be only partially successful and confined to specific molecular constructs. Protection against pH-related degradation can usually be achieved by coating with an acid-insoluble (enteric) coat. Other barriers are more difficult to surmount. Proteins and peptides are usually degraded by proteolytic enzymes in the small intestine such that there have been few successes in oral delivery of macromolecular entities. Consequently, most biopharmaceuticals are administered parenterally.

Rate of passage through the stomach and the intestinal tract may affect rate and extent of absorption. A unit, taken after food (full stomach) is likely to deliver drug later and less consistently to the small intestine, possibly delaying absorption and onset of action. The mechanism of drug action may be such that its effect can be sustained by maintaining plasma levels for longer periods than afforded by its pharmacokinetics. Hence, controlling drug release from the dosage form as the unit transits the gastrointestinal (GI) tract may prolong absorption and subsequent residence at the site of action.

Strategies for prolonging absorption include coating drug with polymeric materials, through which the drug diffuses gradually during gastrointestinal transit. Polymer coatings with pH-dependent solubility may achieve the same effect, drug being released as “pulses” in the intestinal location where polymer is soluble. However, transit rates in the small intestine, while relatively consistent are quite rapid viz 3-4 hours in healthy subjects. This relatively short transit time may mitigate against prolonging an effect if drug is rapidly eliminated and has a short duration of action. Lipidic materials such as oleic can reduce intestinal transit rate to some extent; the so-called “ileal brake” effect, but amounts required generally preclude incorporation in a conveniently-sized dosage form.

Most drugs are absorbed from the small intestine, particularly the proximal region: absorption can be less efficient in distal parts. A possible strategy in such cases might involve retaining the dosage unit in the stomach, drug being gradually released and passed to the intestine, prolonging absorption and extending plasma presence. Such gastro-retention might conceptually be achieved as follows:

- The pyloric sphincter between the stomach and intestine acts as ‘gatekeeper’, retaining larger particles in the stomach until they are suitably digested. A gastro retentive dosage form could be based on dosage unit size. Swellable polymers have been used to coat dosage forms so that unit size increases on ingestion, extending gastric residence. Drug released at a controlled rate from the retained unit sustains delivery to the intestine to prolong absorption; or
- Formulation with mucoadhesive excipients that adhere to gastric mucosa, prolonging residence, drug being released from such units at appropriate rates; or
- Systems based on so-called floating polymers, or on high density beads to provide gastro retention.

Despite such imaginative approaches, gamma scintigraphic and other studies have shown that most if not all gastro-retentive systems perform no better than large non disintegrating dosage units, taken with a meal and possibly in the evening.

Furthermore, the gastric emptying process can be highly variable due to factors such as food (content and nature), posture (standing/prone/sleeping/sleeping orientation) and conditions such as stress, illness and age. Such unreliability could be critical, particularly with medications where consistent onset of action is important. Thus while the goal of prolonged gastric retention is a worthy one the promise remains largely unfulfilled and the strategy has attained little success as commercially viable products.

There have been suggestions that drug-containing microparticles of the requisite dimensions and coated with suitable hydrophilic polymers can lodge in intestinal villi and prolong intestinal residence. However, there is no direct evidence to demonstrate slower intestinal transit.

**PHYSICOCHEMICAL PROPERTIES OF THE DRUG**

**Aqueous solubility:** A drug must be in solution to pass through the intestinal wall. In general terms, if solubility is less than about 1-5 mg/ml absorption might be compromised. However, other factors may need to be explored or considered. Material available for solubility studies, during early discovery and compound selection, may not be in the most thermodynamically stable form, or a mixture of crystalline and amorphous forms. Such materials can be more soluble than the form ultimately used, improvements to purification, isolation, crystallisation techniques providing a more thermodynamically stable but less soluble form that may be less well absorbed. Transformations to these less soluble forms are also possible during material storage or under stresses when processing.

The dynamics of precipitation and dissolution may also be important. A drug with good solubility at gastric pH might be less soluble in neutral environments but may not immediately precipitate in the intestinal milieu; absorption may not be affected. Formation of super-saturated solutions with adequate kinetic stability (solubility) may be feasible using hydrophilic polymers. There can be many exceptions to general maxims relating solubility to absorption. It is important therefore to develop good understanding of factors that contribute to and maintain supersaturation to avoid transformation to the less soluble state.

Low solubility need not necessarily result in a compound being discarded. Strategies to enhance solubility, dissolution rate and absorption include using a more soluble salt, including solubilising excipients in the dosage form, reducing drug particle size among others. Particle size reduction, for instance to micro- or even nano-sized particles can increase dissolution rate, aiding absorption if dissolved drug is readily removed from the drug/dissolving medium interface, allowing more drug to be dissolved. Success is not guaranteed as previously mentioned factors.
such as site of absorption or intestinal transit rate can also be influential. Dose of drug can also be important, a high dose requiring greater volumes of dissolving medium for solubilization. This can complicate development programs where higher doses are tolerated and more effective than originally envisaged from preclinical studies. Dose responses may not be linear.

Permeability:
Passage from the intestine to systemic compartments may involve active transport, absorption via the paracellular route or, in most cases, permeation through intestinal epithelial cells (enterocytes). Drugs best suited to this latter mode of passage are of low molecular mass and relatively lipophilic (log \( P = 1-3 \)). It may be difficult to design molecular structures that accommodate seemingly competing requirements for good aqueous solubility for dissolution (hydrophilicity) and lipophilicity to facilitate absorption. Appropriate hydrophilic/lipophilic balance is also required for passage to organs and tissues that may be the locus of drug activity. It is difficult to design a drug molecule that is “all things to all biological sites”.

INTESTINAL ENZYMATIC BARRIERS

The GI tract is replete with barriers, primed to degrade, transform or otherwise reject chemical, microbial and other harmful agents. Peptide constructs are digested by peptidases in the small intestine. This is a major barrier to oral delivery of macro-molecules such as monoclonal antibodies and other protein-based drugs. Strategies to improve protein and peptide absorption have considered enzyme inhibitors, permeation enhancers, colloidal delivery systems, nanoparticulate systems and many more. All have largely failed. Indeed the wisdom of breaching defense systems to allow peptide and protein passage has been questioned because of the possibilities for opening the route to harmful viruses and the potential for disrupting digestive and absorptive processes for dietary protein.

Intestinal absorption can also be hindered by interactions with the glycoprotein, P-glycoprotein (P-gp) and Cytochrome P450 (CYP450) enzymes in the intestinal epithelium. These can complicate and compromise absorption. Some drugs are also inhibitors of CYP450 enzymes, preventing co-administration. Non-drug materials such as components in grapefruit juice and many herbal materials are also CYP450 inhibitors. These have been considered as formulation aids, to reduce or prevent CYP450 attrition but do not seem to have been used in dosage form design. CYP450 and P-gp enzymes also play major roles in other defense systems, being present in the liver, the blood-brain barrier and other tissues and organs.

In summary, some attractive concepts are available to facilitate or optimise oral dosage. However, variables associated with the GI tract as well as patient-associated variables such as age, lifestyle, smoking, alcohol consumption, even sleep patterns and various co-morbidities, can make oral dosage less than ideal for some drugs and some clinical conditions. Furthermore, for drugs absorbed orally the first port of call is usually the liver. This organ plays a major role in transforming materials to active moieties in the case of prodrugs, or to non-active materials for disposition. Metabolism may also occur in other tissues and organs, reducing or preventing effective drug levels reaching a specific site. Other modes of delivery or targeting may warrant consideration.

NON-ORAL, NON-INVASIVE MODES OF DRUG DELIVERY

The aforementioned vagaries of absorption and metabolic transformation can mean that only a small proportion of the drug dosed orally reaches the biological target. Moreover, drug presence in other tissues or organs can cause unwanted effects. Collateral damage of this nature has probably limited the usefulness of many compounds or arrested their progression. Prime examples concern drugs designed to be cytotoxic to cancer cells but that are also toxic to other organs, tissues or cells.

COX-2 Inhibitors are excellent anti-inflammatory agents but can also cause gastric bleeding; some can also have cardiac side effects.

Parenteral administration provides a more reliable input of drug to the systemic circulation but also leads to hepatic metabolism and can “bleed” the system with drug. It will not be discussed further in this review because of space constraints.

Drugs that may warrant consideration for non invasive delivery that avoids the GI tract must usually be potent as access via “less-travelled” routes is limited, these being designed to protect against ingress of harmful agents. Drug dose needs to be low. Consistency of amount delivered can also be a challenge. Nevertheless, judicious choice of drug, its form and formulation can lead to useful treatments for some clinical conditions.

INTRA-ORAL DELIVERY

Some drugs may be absorbed directly from the oral cavity. Amounts are modest so the route is generally only suited to low dose (potent) drugs. An additional, seemingly mundane but important requirement is that the drug should not be bitter-tasting or have other unacceptable organoleptic properties if used to treat chronic, non-acute clinical conditions. Otherwise, patient compliance may be compromised.

The sublingual region of the oral cavity possesses two vein complexes close to the surface that drain through facial and jugular veins, carrying drug directly to the heart and avoiding hepatic and gastrointestinal tract attrition: the route can be “drug sparing” as a consequence. Absorption is rapid and direct transport to cardiac muscle can provide prompt relief when treating conditions such as angina (gycerlyl trinitrate) or pain. Absorption from the buccal region of the oral cavity is slower so may provide more “controlled release”. Hepatic metabolism is also avoided. Absorption can be sustained over time by formulating as bioadhesive films, possibly release controlling excipients to prolong adhesion and sustain the phar-
macological effect (it is difficult to retain bioadhesive systems sublingually; buccal presence is less intrusive). Dosing can be terminated by removing the film or bioadhesive compact.

Other examples of buccal delivery systems concern chewing gums (nicotine), buccal tablets and “fast-dissolving systems” (see Figure 1).

This route is generally only suited to high potency, low dose drugs due to the limited surface area for absorption, removal of drug in swallowed saliva and the low permeability of buccal tissue. The presence of peptidases within the buccal mucosa is a also barrier to absorption of proteins as is their large molecular mass (low diffusion co-efficients).

Formulation with protease/peptidase inhibitors has been considered but success, in terms of commercial products has eluded researchers to date. A comprehensive review of possibilities and challenges concerning this mode of drug delivery from Repka et al was published in 2011.12

TOPICAL DELIVERY

Topical applications may be used to treat skin bacterial and fungal infections or inflammatory conditions such as psoriasis. Product can be formulated as semi solids (creams or ointments) to prolong contact or as aerosols, foams or sprays for ease of application where skin may be sore. The formulation should be designed such that drug readily partitions from the vehicle to the outer skin layer (stratum corneum), where it may act as a reservoir for diffusion to dermal, sub dermal, possibly subcutaneous locations.

Ideally, there should be little or no systemic absorption although some might reach systemic compartments if skin is damaged, for instance. Preclinical safety studies should take account of such possibilities.

TRANSDERMAL DELIVERY SYSTEMS

Transdermal systems deliver drug through the skin to evince a systemic rather than local effect. Many transdermal medications are designed in the form of an adhesive patch, providing prolonged contact and an accurate delivery area to help dose accuracy.

As a major function of the skin is as a protective barrier there are formidable barriers to this mode of drug delivery. Rate of delivery is slow so contact with the skin needs to be prolonged and the pharmacokinetics or duration of action of the drug should be relatively long. At the same time the “continuous” (zero order) that may be associated with this mode of delivery may suit some clinical conditions or mode of drug action. Peaks and troughs may be avoided and dosing can be terminated by patch removal. It may also be feasible to provide a loading dose of drug by another route (oral/parenteral) with concomitant or follow-up transdermal application to sustain long-term presence at the site of action. Other challenges associated with transdermal delivery can concern skin sensitisation by the drug or by penetration enhancers used in the formulation to improve absorption. Site of application can also determine rate of delivery.

Various techniques and technologies have been developed to enhance transdermal delivery. Organic solvents such as propylene glycol, incorporated in the formulation can disrupt the stratum corneum barrier and improve penetration. Iontophoresis may boost the flux of ionisable structures, a micro current device being incorporated in the application patch. Ultrasound along with “semi-invasive” modes of delivery, such as electroporation, mechanical ablation and perforation using microneedle devices have all been considered as delivery aids.13 Such innovative concepts and activities may reflect the interest in using this route as a (relatively) non-invasive mode of delivering proteins, peptides and oligonucleotides.

Microneedle-based systems are being evaluated as, for example, a means of delivering insulin for diabetes management. However, skin and subdermal layers present formidable metabolic entry barriers. These include peptidases (as well as CYP450 metabolising enzymes) in addition to diffusional barriers (molecular size) to delivery of large molecules.14 The relatively narrow therapeutic index of insulin also requires that amounts delivered be precise. To date no insulin-based transdermal systems are available.

Figure 2 lists examples of some Transdermal medications. A number of other products are also available for hormone replacement therapy, some containing more than one drug. These are not included in the interests of brevity.

INHALATION

Alveolar and associated vascular epithelia are readily permeable, with abundant blood flow and large surface areas for absorption. Drug delivery to such tissue can be effective, particularly in treating local diseases and conditions. Onset of action can be rapid, and gastrointestinal and first-pass / first-attrition avoided. If the site of action is lung tissue there can be a “dose-sparing” effect, with reduced exposure to other sites. Well-established examples concern selective beta agonists such as salbutamol that readily relax bronchial smooth muscle: these are often used in combination with slower acting anti inflammatory agents such as glucocorticoids. Doses by inhalation are in the microgram range, rather than the mg levels required for oral administration that might have more widespread and undesirable long-term effects.

There was much concern when inhaled corticosteroids were first introduced for treating asthma but no significant unwanted effects have been manifested over several decades of use. A major delivery challenge, whether the inhaled medication is in solid or droplet form concerns the tortuosity of the bronchial airways. If particle or droplet size is too large there are losses due to inertial impaction. Particles that are too small fail
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to “settle” and are exhaled. Amounts delivered to alveolar tissue may accordingly be as low as 10-20% of the inhaled dose. Clinical states such as asthma and emphysema can also affect delivery of dose. This has led to the development of sophisticated particle-generating and delivery devices, actuated by inspiration or propelled from an aerosolised container to optimise delivery attributes such as plume geometry and particle velocity, enabling more reliable, accurate and consistent dosing. An additional and important advantage with such delivery devices is capability for dose adjustment, by appropriate technology-based programming of the delivery system, providing a “personalised” dose of medication.

Other considerations for inhalation delivery include potential to elicit allergic reactions in lung tissue (drug or components such as propellants). A drug with irritant properties or which is bitter tasting is also less likely to be suitable for inhalation delivery as taste buds in the pharynx could be impacted on inspiration.

Two insulin-containing aerosol inhalation products have been approved in the US. One was withdrawn because of poor patient acceptance and suggestions, unproven, that it was associated with lung cancer risks due to deposition of insulin on lung tissue. A second product, Mannkind’s Affrezza, was launched recently but long-term sales data is not available at the time of writing. Judgement on non-invasive delivery of insulin has accordingly to be deferred at this time.

INTRANASAL DELIVERY

Advantages associated with intranasal delivery concern high permeability of nasal epithelia for hydrophobic drugs, an extensive underlying vascular bed, avoidance of “first-pass” hepatic metabolism and of gastro intestinal attrition.

The susceptibility of biopharmaceutical products to degradation when dosed via the GI tract, along with their increasing prominence as medicinal agents has spurred much interest in non-invasive routes for delivering these to systemic compartments. The intranasal route is no exception. However, permeation of polar drugs and macromolecular entities like proteins and peptides is low. Furthermore, the nasal airways are designed to protect pulmonary tissue from hazardous materials and to hinder systemic absorption. Aerodynamic behaviors and anatomical features of the nasal regions, with the majority of droplets deposited in the anterior nasal mucosa due to inertial impaction and sedimentation present significant barriers to efficient delivery. Ciliary motion and a protective mucous layer designed to intercept particles, microorganisms and other unwanted materials are additional hurdles. The nasal cavities can be highly sensitive to the presence of irritants; sneezing in response to a stimulus can expel a medication. The enzymatic barriers in the nasal epithelium are also similar to those hindering other modes of systemic entry: CYP450 enzymes are present at even higher levels than in liver. Peptidases and proteases are also present.

Reliable and efficient delivery of protein-based biopharmaceuticals by this route may be as challenging as for other non-invasive modes of dosage. So-called absorption enhancers have been evaluated as a means of increasing amounts of drug that are absorbed. These present their own challenges. Bioadhesives to prolong contact may also cause mucosal damage if usedchronically.

Vaccines can be administered intranasally as there is potential for inducing superior antibody response in the upper respiratory tract. They may be formulated as a spray mist containing muco-adhesive polymers, adhesion to the nasal mucosa improving immune response. Available space prevents discussion of other modes of non-invasive delivery such as rectal, ocular, vaginal, and colonic delivery.

FUTURE PERSPECTIVES

The locus of activity for many medicines may be within a specific organ or cell type and precise targeting by molecular design may not be feasible. In such cases drug delivery strategies warrant consideration. Two topics are considered here, namely delivery to the brain and intracellular targeting to illustrate delivery concepts being considered. These should be viewed as illustrative as they do not represent the extent of activities in the area. Many other innovative approaches are also being explored.

DELIVERY TO THE BRAIN

Anxiety, Depression, neurodegenerative conditions such as Alzheimer’s and Parkinsonism, eating disorders, drug addiction and other clinical conditions are considered to be brain-associated. Neurodegenerative conditions in particular respond poorly to current medications. This has serious sociological and societal implications for future healthcare. Dementia-related conditions increase exponentially with age; almost 40% of people aged 75-84 or older in the US are estimated as suffering from Alzheimer’s disease.

Total healthcare spending on geriatric healthcare currently consumes approximately 16% of US GDP, 75% being spent on treating chronic illnesses. Longer lifespans are likely to inflate such numbers. Trends in many other countries are probably similar. Societal burdens could become immense.
The less-than-stellar records of many current medications may be due inadequate levels of drug reaching the site of activity. The blood-brain barrier (BBB) presents formidable hurdles to passage of many agents, particularly those that are polar in nature. It has been estimated that more than 98% of current drugs do not surmount this hurdle to any significant extent.21

The BBB is more readily crossed by non-polar (lipophilic) entities but these are likely to be poorly absorbed from the GI due to their low solubility, or are metabolised in hepatic and other locations to polar structures for ready elimination. Consequently, drug discovery programs have focused to some extent on providing water-soluble drugs. Plasma protein binding also militates against brain delivery.

Drugs administered by the oral route and others already discussed in this paper are invariably transported via the bloodstream (lymph in some instances). They encounter the BBB so passage to the brain is limited. Molecular design may help lower the barrier but higher doses may be required so that sufficient passes to the brain. This may lead to “drug overload” and side effects in other organs and tissues throughout the body. Consequently there is much interest in strategies for better-targeted brain delivery.

One possibility, meriting consideration concerns passage from the upper nasal cavity via trigeminal and olfactory pathways, thereby avoiding the BBB.20,24 Aromatherapy, based on using volatile oils and other aromatic compounds as mood-altering agents is based on such concepts. Vapours rapidly reach the brain and a much lower dose than delivered conventionally might provide effective therapy if drug could be delivered as vapour.

Figure 3 provides a schematic for disposition and fate of drug administered intranasally. A fraction may be eliminated by degradation or mucociliary clearance, more may be absorbed through the anterior nasal mucosa, or by swallowing. Absorbed materials encounter and are largely recycled (rejected) at the BBB. A fraction may reach the upper nasal region and, if in suitable form, some may enter the brain via the olfactory and trigeminal conduits.

Thus, mucociliary clearance, enzymatic degradation, swallowing, possibly other modes of disposition are likely to reduce amounts reaching the upper nasal cavity. Furthermore, drug in solution or particulate form may not be in a suitable state to enter the olfactory/trigeminal pathways are unlikely to facilitate passage of liquids or solids (the usual way to effect delivery). These are structured to allow passage of vapours. Ideally, potentially useful drugs for delivery by the nose-to-brain route would be in the vapour state but few drugs are likely to have been designed with such properties in mind. Crystalline solids of good purity are usually favoured in drug discovery and development, ideally in soluble form for acceptable oral absorption.

There is evidence that brain pathology associated with conditions such as Alzheimer’s disease, depression and Parkinsonism may be related to chronic inflammatory processes. It has also become evident that the nonsteroidal anti-inflammatory agents, COX-2 Inhibitors appear to be beneficial in such conditions.21,25,26

However, small pilot trials with NSAIDs dosed orally, while providing encouraging results with Alzheimer’s patients, were compromised by high dropout rate due to GI side effects.27,28

Other trials provided similarly confounding results. It would seem that the GI and other side effects of NSAID’s dosed orally would constrain their use for treating or preventing such chronic conditions. However, better targeted delivery to the brain via the upper nasal cavity could avoid widespread disposition in other tissues, require much lower dosage and have a significantly better side effect profile.

The NSAID ibuprofen, and possibly other NSAID’s, reportedly exhibit vapour pressure.29,30,31 Evidence of volatility of other drugs is somewhat lacking but few existing drugs would have been intentionally designed to be volatile. It is possible, however, that other well-established drugs could be isolated in volatile form; free base or acid rather than salt for instance.

There may be scope for innovative chemistry to provide material in a volatile form that retains its molecular integrity. Functional requirements for so-called odorants have been defined in terms of vapour pressure, polarity, lipophilicity and surface activity.32 Such definitions might provide useful templates for molecular design, or searches for existing agents.

Other possibilities for facilitating brain entry via olfactory/trigeminal routes might utilise solutions of drug in propellants of the kind currently used for lung delivery of anti-asthma medications. The rapid vaporisation of such propellants might leave drug in vapour form for sufficiently long for passage to the brain to occur.

"Ideally, potentially useful drugs for delivery by the nose-to-brain route would be in the vapour state but few drugs are likely to have been designed with such properties in mind. Crystalline solids of good purity are usually favoured in drug discovery and development, ideally in soluble form for acceptable oral absorption"
Nanobots (“nanobots”) have been conceived and designed with such requirements in mind, being assembled from DNA strands. DNA nanobots, in addition to being “biocompatible” also have valuable “design capability”, a long single strand of DNA being capable of coupling with shorter strands to provide a suitably “sized and shaped DNA cage” to accommodate a drug. “DNA hinges” in such clams-shell-like constructs provide capability to exist in open or closed form (see Figure 4a & 4b). The closed shell, in conjunction with anchor strands within the cage and complimentary DNA linker strands attached to the drug, secure drug retention. The cage is locked by DNA double helices.34

The external surface of the nanobot is designed to recognise and dock only to cancer cells. On cell entry by the nanobot, a cancer specific protein within the cell “unlocks the cage” to release drug in a “trojan horse-like” manner. Such constructs have been shown in vitro to target a series of six different cancer cell lines: cage-constructs have been shown in vitro to target a specific drug. There is no “one size fits all”. This review has accordingly focused on the limitations as well as the possibilities for dosage-form design so that informed choices can be considered in oral formulation programs. There is also much interest and associated activity in concepts that may provide more precise and localised drug delivery to render such materials more effective and safer. Such insights, along with better diagnostic concepts and technologies can greatly help in assessing the utility of novel constructs as drugs or in improving the performance of those already being used.

CONCLUSIONS

Systems that are currently available to target or modify the delivery of drug have advantages and limitations that can be associated with the clinical condition, the patient or the molecular biology/mode of action and physical characteristics of the specific drug. There is no “one size fits all”. Many other innovative approaches, too numerous to reference here, are being pro-

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Introduction

INTRODUCTION

The potential of therapeutic peptides to address a growing range of diseases has gained increasing recognition in recent years. Due mainly to their poor stability and short plasma half-life, peptides are usually administered by injection, often several times daily. Injectable sustained-release formulations of peptides demonstrated the power of drug delivery technologies to enhance patient adherence and convenience, and increase safety and efficacy. However, the pain and invasiveness of injections, as well as disposal issues associated with used needles and relatively complicated administration protocols mean that alternative routes of delivery are highly desirable for peptides.

Various approaches have been designed to overcome these barriers including absorption enhancers, conjugation or chemical modifications, enzyme inhibitors and mucoadhesive polymers, often in combination. Although for the most part, the obtained bioavailability remains very low, many of these approaches are showing promising results in clinical trials, with some products getting close to market. Furthermore, there is still a need to propose enhanced approaches able to overcome issues encountered during oral peptide delivery such as food effects and intra-subject variability.

PARTICULAR CONSIDERATIONS FOR ORAL PEPTIDE DELIVERY

Pharmaceutics Considerations

Peptides make attractive drug candidates due to their specificity, potency and low toxicity, but present particular challenges for their delivery to the site of action, due to their short half-life and susceptibility to proteolytic degradation. Their relatively high molecular weight and (usually) high hydrophilicity limits their permeability across epithelial membranes. The effect of the pH range encountered in the gastro-intestinal (GI) tract on both their stability and solubility warrants careful design of any oral delivery system. Furthermore, as they are potential substrates to the plethora of enzymes in the GI tract, a significant portion of the delivered dose is likely to be digested even before it reaches the epithelial membrane.

It should be noted, however, that some peptide structural properties can have a strong impact on their stability in the GI tract and oral absorption. For instance, it seems that cyclic peptide structures show improved stability in the GI tract, making...

“We to some extent, the need for larger quantities of a therapeutic peptide for oral administration (compared with the quantity required for injection) could be counterbalanced by the absence of need for aseptic manufacturing and the decrease in the cost/g when production scale increases”
them better candidates for this route of administration. Furthermore the propensity of some peptides to self-assemble or aggregate adds an additional level of complexity to their delivery, as it would be expected that any such aggregates would be less likely to be absorbed, and strategies to prevent aggregation may need to be employed.

To address these issues, a number of formulation strategies have been developed, the most advanced of which is the use of various excipients to control delivery of the peptide to specific sections of the GI tract (e.g. enteric coatings), absorption enhancers, and enzymatic inhibitors, often in combination. The need to deliver the peptide to the epithelial membrane together with the absorption enhancer and enzyme inhibitor means that often the effectiveness of these systems is significantly adversely affected by food effects.

The patient experience and perception of the dosage form will also have an impact on patient adherence to the treatment. For example, Fransen et al (Pharm Res, 2009) showed that patients preferred nasal desmopressin over the sublingual form because they considered it faster and simpler, and also because the sublingual form disintegrated too slowly. This study highlights the need for careful design of the formulation with the end-user in mind.

PATHOPHYSIOLOGY, PHYSIOLOGY & PHARMACOLOGY CONSIDERATIONS

Diseases that affect the functioning of the GI tract may impact upon the suitability of the oral delivery route and the effectiveness of the delivery system. For example, swallowing ability, GI tract secretions (e.g. enzymes, bile), the integrity of the epithelial barrier, the mucus barrier and transit time can all be effected by various diseases and would be expected to have an impact on the performance of the delivery system and suitability of the oral route.

In addition, the presence of receptors for the API in the GI tract may impact the safety and tolerability of the peptide delivered orally, and their function and pharmacology should be understood and any implications considered.

Finally the first-pass effect has also to be taken into account. Not only might this limit the systemic availability of the delivered API, but it could offer a compelling case for positively impacting upon efficacy as a number of proteins and peptides act on the liver (e.g. insulin, glucagon-like-peptide-1 (GLP1) analogues, and human growth hormone (hGH).

END-USER CONSIDERATIONS

Prior to the development of an oral formulation, demographic factors including end-user age and culture should be considered. For example, in China it has been reported that there is a high prevalence of the use of the intravenous route, the reasons for which are complex, but include patient perception of treatment efficacy.

For patients who fear injections and express a “needle phobia”, oral formulation may improve convenience and compliance. However, the decision-making process is not always so simple, particularly bearing in mind the availability of sustained-release formulations of peptides – would patients prefer to take a tablet twice a day for the rest of their life or have an injection once every six months and forget about their disease?

Even if the oral route is the most preferred route of administration, safety and efficacy of the treatment by the patient is paramount over the route of delivery. For example, Flood et al evaluated the importance to patients of the product attributes of a nasal vaccine versus the injectable, and found that safety and efficacy were the most important and the route of delivery secondary. It is therefore essential that safety and efficacy of any oral peptide formulation is maintained, in addition to any improvement in patient adherence.

ANTICIPATING THE SWITCH INJECTABLE TO ORAL

The main issue in the development of peptide therapeutics for oral delivery is the low and variable oral bioavailability. More precisely, the oral route shows a very low absolute bioavailability of only a few % in humans. As a result, the dose and frequency of dosing need to be increased in order to keep plasma concentration within the therapeutic window and ensure drug efficacy. It should therefore be anticipated that both the cost of goods (CoGs) of the unit dose and the quantity of active pharmaceutical ingredient (API) to be manufactured will strongly increase.

This might therefore require significant investment to increase manufacturing capacity to fulfil the increased API demand. To some extent, the need for larger quantities of a therapeutic peptide for oral administration (compared with the quantity required for injection) could be counterbalanced by the absence of need for aseptic manufacturing and the decrease in the cost of API/g when production scale increases.

Finally, if more expensive than the injectable form, reimbursement of the oral treatment should be considered, and its benefits may need a strong justification – reinforcing the need for safety and efficacy to be at least similar, but preferably improved, compared with injection.

APPROACHES & STRATEGIES USED FOR ORAL PEPTIDE DELIVERY

Tremendous efforts have been dedicated over numerous decades to delivery of peptides by the oral route, and a plethora of different strategies have been proposed aimed at improving the permeation of the peptide through the intestinal membrane, protecting it against enzymatic degradation and the harsh environment of the GI tract.

The principle approaches consist of:

- co-administration of permeation enhancers and protease inhibitors
- covalent conjugation with chemical or biological entities that show cell-penetrating capabilities, such as bacterial toxin, cell penetrating peptides
- design of multifunctional drug delivery systems that help peptide trafficking through the cells such as functionalised nanoparticles (with e.g. Fc fragments, vitamin B-12, transferrin), microparticles and liposomes
- design of muco-adhesive or gastroretentive delivery systems which prolong the residence time of the drug in the GI tract.

ABSORPTION ENHANCERS

The oral absorption of a peptide can be improved by co-formulation with permeation enhancers that promote the crossing of the epithelial membrane involving the combination of several mechanisms, such as:

- (a) increased paracellular permeability by reversible opening of the tight junctions; this can be achieved for instance by fatty acids, toxins like Zonula occludens toxin (ZOT), and chelating agents; (b) increased transcellular permeation by increasing membrane fluidity, which can be achieved by a surfactant  or improving binding and uptake of the peptide by the epithelial cell and trafficking through the cell, e.g. using Fc-targeted...
nanoparticles; and (c) decreased mucus viscosity, e.g. using bile salts. Other excipients have been shown to improve permeability by bioadhesion, such as chitosan and thiolated chitosan. However, they are also suspected to exhibit tight-junction modifier properties, which means that their mechanism of action might not be fully understood.

Despite their proven efficacy, permeation enhancers may have potential toxic effects on the intestinal cells due to the high concentration needed in the formulation and their chronic use for long periods of treatment. This toxicity may result in membrane inflammation, membrane erosions and intestinal epithelium ulceration. In addition disrupting the lipid bilayer increases its permeability to drugs, but also to other pathogens which may result in infections and immunological reactions. That said, the intestinal epithelium is actually relatively robust (versus the nasal epithelium, for example) and is constantly renewing itself, so any cellular damage is generally transient.

**PEPTIDASE INHIBITORS**

Another key challenge in oral peptide delivery is to ensure their protection against the degradation induced by various types of endopeptidases (such as pepsin, trypsin, chymotrypsin, elastase) and exopeptidases (such as carboxypeptidases A and B). Agarwal et al reported the use of chicken and duck ovomucoids as enzyme inhibitors protecting insulin from trypsin and a-chymotrypsin digestion. A Serine protease inhibitor, Serpin, can form covalent complexes with protease and thus protect peptides from peptidase attacks. Other studies demonstrated the potential of aprotinin and soybean trypsin inhibitors, camostat mesilate and chromomustin as enzyme inhibitors.

Although enzyme inhibitors significantly improve peptide stability in the GI tract, they can disturb the digestion of nutritive proteins and peptides, and as a result of the feedback regulation, stimulate peptidase secretion.

**EXAMPLES OF CLINICAL-STAGE TECHNOLOGIES FOR ORAL PEPTIDE DELIVERY**

**Peptelligence®**

Initially Unigene and then Enteris Biopharma (Boonton, NJ, US) developed this technology based on an enteric-coated tablet, whose core formulation contains, in addition to the peptide, an organic acid enzyme inhibitor (citric acid in the form of coated beads) and a permeation enhancer (acylcarnitine) which is claimed to help penetrate the mucus layer. The coating of the organic acid granules prevents acid degradation of the peptide in the tablet during storage.

Oral formulations of salmon calcitonin using Peptelligence® technology completed a randomised, double-blind, double-dummy, active- and placebo-controlled multiple-dose Phase III clinical trial in 565 post-menopausal osteoporotic patients. It was found that the oral calcitonin formulation achieved improved efficacy versus the marketed nasal spray (i.e. greater increase in lumbar spine bone mineral density), probably due to the increased systemic peptide exposure.

In addition, Peptelligence® was also used to develop an oral formulation of parathyroid hormone (PTH) that completed a Phase II clinical trial in osteoporosis compared with the reference injectable product on the market (Forteo®). It was shown that the pharmacokinetics were highly reproducible and oral PTH formulation increased bone density, although in this case efficacy was reduced compared with reference injectable treatment.

**TRANSIENT PERMEATION ENHANCER**

Chiasma, Inc (Newton, MA, US) is developing transient permeation enhancer (TPE) technology for the oral delivery of octreotide (Octreolin®). TPE technology is an enteric-coated liquid-filled capsule containing an oily suspension of the drug and sodium caprylate in hydrophilic microparticles that are mixed with castor oil or a medium-chain glyceride and/or caprylic acid. Sodium caprylate is claimed to provide a transient opening of the tight junctions providing enhanced paracellular peptide absorption. Chiasma completed Phase III clinical trials of oral octreotide (Octreolin®) using TPE technology. Chiasma claims that the TPE technology protects the peptide from enzymatic digestion and transiently opens tight junctions.

It was demonstrated that an oral dose of 20 mg octreotide using TPE technology, can achieve similar pharmacokinetics as 0.1mg octreotide SC (a relative oral bioavailability of less than 1%). It was also shown that bioactivity of the peptide is preserved, since the oral administration of octreotide led to the expected suppression of growth hormone (GH) secretion following a growth hormone-releasing-hormone (GHRH) induction test. However, food effects or drug-drug interactions were also observed: taking the Octreolin® capsule after a meal or with a proton pump inhibitor (like esomeprazole) led to gastric pH changes, significantly affecting oral absorption of the peptide.

In a multicentre Phase III clinical trial, 155 adults with acromegaly receiving injectable somatostatin analogs for three months were switched to oral Octreolin® containing 20 mg of octreotide twice-a-day and were evaluated for biochemical and symptomatic disease control for up to 13 months. Doses were escalated to 60 and then up to 80 mg/day to control insulin-like growth factor-1 (IGF-1). Once fixed the doses were maintained for a seven-month core treatment followed by a voluntary six-month period. Octreolin® demonstrated significant efficacy in controlling IGF-1 and GH concentrations for 13 months. In fact this efficacy was achieved in 65% of patients at the end of the core treatment period and in 62% patients at the end of the treatment. In addition, the effect was durable in 85% of the 91 patients initially controlled on oral Octreolin® with a sustained response for 13 months. These results are comparable with those reported for 41 acromegaly patients responding to injectable octreotide LAR, 84% of these maintained baseline IGF-1/GH control at six months. In addition, during this study it was observed that the incidence of adverse events significantly decreased over time, suggesting that the safety profile of Octreolin® is consistent with the profile of injectable octreotide formulations.
MERRION’S GIPET® TECHNOLOGY

Merrion Pharmaceuticals (Dublin, Ireland) is developing the GIPET® technology using an enteric coating (similar to Peptelligence® and TPE technologies), in order to protect the peptide in the acidic gastric medium and ensure peptide release in the small intestine. This technology is based on the use of medium-chain fatty acids, in particular sodium caprate, which is claimed to open tight junctions transiently. Merrion has a partnership with Novo Nordisk and the companies have completed Phase I trials using GIPET® to deliver both insulin and GLP-1 analogues.18

ELIGEN® TECHNOLOGY

Emisphere Technologies (Roseland, NJ, US) has developed various types of oral formulations including solutions, tablets, and capsules, based on the Eligen® technology. This technology uses SNAC (sodium N-[8-(2-hydroxybenzoyl)amino] caprylate or salcaproate sodium), 5-CNAC (N-(5-chlorosalicyloyl)-8-aminocaproic acid), 4-CNAB (4-[4-chloro-2-hydroxy-benzoyl]amino]butanoic acid) and SNAD (N-(10-[2-hydroxybenzoyl]amino)decanoic acid) as absorption enhancers. These excipients were claimed to form non-covalent complexes that protect them from digestive enzymes and improve the crossing of peptides and proteins through the intestinal epithelium through a transcellular pathway. In addition, it was claimed that unlike the traditional penetration enhancers, SNACs do not cause histological damage to the intestinal epithelium. SNAC achieved generally recognised as safe (GRAS) status for its intended use in combination with nutrients added to food and dietary supplements.19

Furthermore, the first product Eligin B12™ using SNAC in order to improve the absorption of vitamin B12 is now on the market.20 Also, Eligen® technology completed Phase I clinical trials and has shown promising results for oral delivery of various peptides and proteins such as insulin, recombinant human growth hormone (rGH), calcitonin and recombinant parathyroid hormone (rPTH).

PROTEIN ORAL DELIVERY TECHNOLOGY POD™

POD technology developed by Oramed (Jerusalem, Israel), consists of enteric-coated capsules containing an oily suspension of the peptide drug, an enzyme inhibitor, such as soy bean trypsin inhibitor, aprotinin and an absorption enhancer such as EDTA or bile salt, in omega-3 fatty acids. This technology was used to develop an oral insulin pill, which recently completed a Phase IIa clinical trial and is progressing into Phase IIIb. It was reported that POD technology including insulin administered pre-prandially three times daily, in conjunction with daily subcutaneous insulin was safe and well tolerated. In addition, POD technology significantly reduced glycaemia in a small cohort of patients with uncontrolled type 1 diabetes.21

NOD TECHNOLOGY

NOD is an oral peptide technology developed by Novo Pharmaceuticals (Shanghai, China), which is now entering Phase I. The technology includes enteric coated and bioadhesive calcium phosphate nanoparticles (5-200 nm in size) in the final dosage form of a capsule. The NOD formulation is obtained by mixing exenatide with calcium phosphate in the presence of PEG salts of fatty acids (e.g. caprylate, sodium caprate) or bile salts as precipitating agents (cholate, deoxycholate, taurocholate, glycocholate, taurodeoxycholate, ursodeoxycholate, tau-roursodeoxycholate, and chenodeoxycholate). The obtained calcium phosphate nanoparticles may be enteric coated by using cellulose acetate phthalate, and also contain a bioadhesive polymer such as a carbomer.22

MIDATECH’S GOLD NANOPARTICLES

This technology from Midatech Pharma (Abingdon, UK) offers the possibility

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**Table summarising selected oral peptide delivery technologies.**

<table>
<thead>
<tr>
<th>Company</th>
<th>Lead Peptide</th>
<th>Technology Name</th>
<th>Technology composition</th>
<th>Formulation</th>
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<tr>
<td>Enteris Biopharma</td>
<td>Calcitonin</td>
<td>Pептилінгезе</td>
<td>Absorption enhancer (acyl carnitine) and enzyme inhibitor (organic acid: citric acid)</td>
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<td>Tarsa Therapeutics</td>
<td>Phase III</td>
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<tr>
<td>Chiasma</td>
<td>Octreotide</td>
<td>TPE</td>
<td>Suspension of drug particles in oils and absorption enhancer (caprylic acid, C8, castor oil, medium chain)</td>
<td>Capsule</td>
<td>Roche (discontinued)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Oramed</td>
<td>Insulin and exenatide</td>
<td>POD</td>
<td>Peptide with absorption enhancer (e.g.EDTA) and protease inhibitors (e.g. soya bean trypsin inhibitor, EDTA) enteric coated tablet/capsule</td>
<td>Capsule</td>
<td>Novartis</td>
<td>Phase II</td>
</tr>
<tr>
<td>Merrion Pharmaceuticals</td>
<td>Insulin and GLP-1 analogues</td>
<td>GIPET</td>
<td>Absorption enhancer: medium chain fatty acids (sodium caprate) as a</td>
<td>Tablet</td>
<td>Novo Nordisk</td>
<td>Phase I</td>
</tr>
<tr>
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<td>NOD</td>
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<td></td>
<td>Phase I</td>
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<tr>
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<td>Insulin and GLP-1</td>
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<td>Surface modified gold nanoparticles complexed with peptides</td>
<td>Adhesive buccal patch</td>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td>Rani Therapeutics</td>
<td>Insulin and GLP 1 analogues</td>
<td>Robotic pill</td>
<td>Balloon-like structure outfitted with hollow micro needles made of sugar and preloaded with peptides</td>
<td>Capsule made of biodegradable material (e.g. PLGA)</td>
<td>Novartis</td>
<td>Preclinical</td>
</tr>
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Figure 1: Table summarising selected oral peptide delivery technologies.
Figure 2: Schematic diagram of "robotic pill" concept comprising a capsule containing chemical compartments composed of citric acid and sodium carbonate in two chambers separated by a valve, and an inflatable balloon-like structure with hollow micro needles made of sugar and preloaded with the therapeutic peptide.

CONCLUSIONS

From a patient perspective, the oral delivery route is simpler and more convenient when compared with the injectable route. However, a number of challenges are associated with oral peptide delivery including low stability in the GI tract and low oral bioavailability – related to low permeation through the intestinal epithelium and inactivation and proteolytic degradation in the GI tract.

Several strategies and technologies have been invented (a selection is summarised in Figure 1) to overcome these challenges and these have made it possible to progress new oral peptide products into the clinic, with many now in late stage development.

Relative bioavailability is still low though, even with the most advanced state-of-the-art technologies, limiting their application to high potency peptides with large therapeutic windows. Furthermore, the most advanced technologies still suffer considerable food effects, and drug-drug interactions – an issue which, if addressed, could significantly improve on the currently available technologies.

A very novel approach based on intra-enteral injection has been developed recently by Rani Therapeutics (San José, CA, US) to deliver peptides via the buccal route, which avoids the outcomes encountered when delivering via the intestine. In fact, Gutniak et al showed that an adhesive buccal patch containing GPL-1 achieved a bioavailability in man of 47%. In this way, Midatech developed a similar buccal patch delivering insulin from gold nanoparticles. This technology successfully completed Phase I in healthy volunteers and now is moving into a Phase II trial in patients.

Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its development strategy is supported by three franchises: neurology, endocrinology and urology-oncology. Ipsen's commitment to oncology is exemplified through its growing portfolio of key therapies improving the care of patients suffering from prostate cancer, bladder cancer or neuro-endocrine tumours. Ipsen also has a significant presence in primary care. Moreover, the group has an active policy of partnerships.

Ipsen's R&D is focused on its innovative and differentiated technological platforms, peptides and toxins, located in the heart of the leading biotechnological and life sciences hubs (Les Ulis, France; Slough/Oxford, UK; Cambridge, MA, US). The Group has more than 4,500 employees worldwide.

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Andy Lewis, PhD, is Director of Novel Drug Delivery Technologies at Ipsen where he leads the development of new products utilising innovative delivery technologies for their peptides portfolio. Prior to joining Ipsen he helped set up and grow two venture capital-funded start-ups, RegenTec and Critical Pharmaceuticals, where he lead the development and commercialisation of novel technologies in the fields of tissue engineering and drug delivery, taking them from concept into clinical development. His work has focused on the delivery of macromolecules, particularly the sustained release and transmucosal delivery of proteins and peptides, and he has filed a number of patents in the field. He is a member of the Academy of Pharmaceutical Scientists of Great Britain, and has served on the Membership Committee, Board of Scientific Advisors and for the last three years he has been Director-at-Large of the Controlled Release Society (CRS).

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Joël Richard, PhD, has more than 25 years’ experience in industrial R&D, including several global senior positions in various biotech and pharma companies. Dr Richard is currently Senior Vice-President, Peptides, at Ipsen. He is globally leading
all the CMC development activities of both injectable peptide products and oral small molecules, including APIs and drug products, with major franchises in Oncology, Endocrinology and Neurology. Dr Richard graduated from Ecole Normale Supérieure in Cachan, France. He gained a PhD in Materials Science from the University of Paris, France. In the last 15 years, Dr Richard has focused his research activity on new formulation and drug delivery technologies, especially for injectable protein and peptide formulations. Dr Richard has published 65 peer-reviewed scientific papers, eight book chapters and two review editorials in various fields (colloids and interfaces, drug delivery, supercritical fluids, protein formulations, sustained-release formulations etc). He is the author of more than 100 international communications and 53 patent families.

REFERENCES

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Q: Why is taste-masking important?
A: Many active pharmaceutical ingredients (API) inherently possess a bitter taste. Nearly 20% of American adults surveyed complained of bad aftertastes or struggling to swallow when trying to take medication.1

If a medication is not palatable, the patient may opt to discontinue it. In fact, one of our own colleagues admitted he would rather risk malaria than continue with the foul-tasting preventative regimen. Whilst that comment might sound flippant, in fact it illustrates a very serious problem. Failure to take medication as prescribed leads to increased morbidity, mortality, and potentially avoidable healthcare costs exceeding US$100 billion annually in the US alone.2 While objectionable taste may be one of several reasons for poor adherence, every measure that minimises these reasons helps.

With a recognised impact on patient healthcare outcomes and costs, the European Medicines Agency (EMA) has released guidelines promoting the development of medicines for paediatric use.3 The US FDA is promoting similar initiatives. As a result, Colorcon has seen an increased interest from the pharmaceutical industry in taste-masking technologies.

Q: Which populations are most commonly targeted for taste-masking?
A: As you would imagine, taste-masking is incredibly important for paediatric populations. Firstly, children are 3-4 times as sensitive to tastes as adults, with increasing tolerance to bitter tastes with age. Secondly, children, particularly infants, are unable to rationalise ingestion of an unpalatable medicine. Geriatric patients also often have problems with adherence due to difficulty in handling and swallowing tablets. While crushing some immediate-release tablets may be allowable, it generally is not advisable, or palatable, and so other dosage forms may be more desirable.

Q: What criteria are important for taste-masked formulations?
A: Both dissolution profile and taste profile contribute to the acceptability criteria for taste-masked formulations. However, each drug product will have different release profile requirements to meet an acceptable level of taste-masking depending on the dose strength and organoleptic response to the API. Ideally, the taste-masked dosage form should prevent release of the unacceptably tasting medicine until the API has left the mouth, then allow for immediate release once the dosage has been ingested.

To determine the taste profile, while electronic tongue technology is advancing, taste panels remain the preferred method for determining efficacy of taste-masking. Patients may be able to tolerate different levels of release in the mouth for different APIs depending on the drug solubility and other ingredients such as flavours and sweeteners in the formulation. Some regulatory authorities have cautioned that the formulation cannot taste “too good” as a safeguard against mistaking the medication for candy. Taste profiles should aim for a neutral taste or one that is generally acceptable.

Mouthfeel can also contribute to the acceptability of a dosage form. If a drug particle or granule is tasteless but too large, it can give an unpleasant gritty sensation. Larger particles also become targets for chewing, eventually crushing the taste-mask coating, and causing release of the drug and bitter taste in the mouth.

Specifically in the case of paediatric dosage forms, the goal for taste-mask coating aims for the minimum weight gain necessary to achieve robust functionality. However, effective weight gains will be dependent on the properties of the substrate. For instance, if the drug particle is very fine or has a broad particle size distribution, higher weight gains of the
coating will be required for consistent taste-masking. In short, when it comes to successful taste-masking, understanding the properties of your coating substrate or drug really matter.

Q: What kinds of strategies are available for taste-mask formulations?
A: For most solid oral dosage forms (SODs), the API is blended with a number of excipients, and a well-designed film coating, such as Opadry® complete film coating system, often provides sufficient properties to adequately mask objectionable tastes for the brief residence time in the mouth before swallowing.

Alternative dosage forms such as sachets, ODTs, and chewable dosage forms pose additional challenges in taste-masking due to increased contact surface area as well as residence time in the mouth, enhancing any unpleasant taste and/or lingering aftertaste. In these cases it is often necessary to create a barrier, such as a specific taste-mask coating, between the API and the taste buds in order to improve palatability and aid compliance.

In a review of taste-masking technologies, coating was most highly rated, with inclusion of flavours and sweeteners a close second in terms of popularity (Figure 1).

Q: What types of coating technologies exist that provide taste-masking for oral dosage forms?
A: There are two main categories of coatings for taste-masking: pH-independent and pH-dependent.

As an example of a pH-independent taste-mask coating, Colorcon’s customers have been successful when a combination of Surelease® and Opadry® is applied. Surelease is an aqueous ethylcellulose dispersion and acts as the insoluble barrier membrane which prevents drug release in the mouth. Opadry acts as the soluble pore-former to promote immediate release in the stomach.

Recent work at Colorcon has demonstrated the use of this combination for taste-masking acetaminophen (APAP) granules. Surelease:Opadry (85:15) was applied to APAP granules in a Glatt GPCG-2 fluid bed. Granules were coated to 10% weight gain of the Surelease:Opadry and compressed into a chewable tablet formulation. The dissolution profiles are shown in Figure 2, demonstrating that by using Surelease and Opadry for taste-masking we were able to match the release profile of a commercially marketed product and meet requirements for immediate release (no less than 75% released in 45 minutes).

You may have noticed that the dissolution of the coated granules is quite different before and after compression into the chewable tablet. It is completely normal and expected for a partial rupture of the coating upon compaction pressure, and this can be accounted for in the design of the dosage form, as we have done here.

The second category of taste-mask coating technology is a pH-dependent coating based on reverse enteric polymers which are insoluble at the relatively neutral pH of the mouth and become soluble once in the lower pH of the stomach.

Included in this class of polymer are acrylic acid soluble polymers such as...
Kollicoat® SmartSeal, an aqueous dispersion of methylmethacrylate and diethylaminoethyl-methacrylate copolymer from BASF (Ludwigshafen, Germany). The product was developed specifically for taste-masking applications for orally administered pharmaceutical products, and is considered a best-in-class reverse enteric polymer.

In 2014, Colorcon entered into a collaboration with BASF to develop a fully formulated coating system using Kollicoat SmartSeal. This relationship leverages BASF’s expertise in polymer chemistry and Colorcon’s long-recognized leadership in fully formulated coating systems for pharmaceutical use. This collaboration aims to improve manufacturing speed and simplicity for the customer, enabling easy reconstitution of the film former while maintaining product functionality.

Colorcon is excited to have expanded its taste-masking product portfolio with Kollicoat SmartSeal. This allows us to better serve the industry in providing solutions to improve adherence, particularly in the more challenging pediatric and geriatric spaces.

Q: What is the regulatory status of these coatings?
A: Surelease and Opadry have been used for decades in the pharmaceutical industry including in immediate and extended release systems. Surelease has precedence of use in the US and EU for both adult and pediatric formulations.

In fact, the combination of Surelease and Opadry was selected by Merck, Sharpe, and Dohme (MSD) for a taste-masked version of ISENTRESS (raltegravir) for the treatment of HIV specifically for the paediatric segment.7

Kollicoat SmartSeal is a relatively new polymer in the marketplace, and its safety is supported by a comprehensive toxicological package including both in vitro and in vivo studies. There has been considerable interest from multinational pharmaceutical companies to explore SmartSeal for taste-masking development projects. Colorcon’s regulatory team is also poised to assist any customer through the commercialisation process.

Q: What are the main concerns in the industry around taste-masking?
A: Some in the industry are concerned that a taste-mask coating could slow or completely arrest release, affecting bioavailability or efficacy of the drug.

Transit times in the gastrointestinal tract can vary greatly depending on the age of the patient, whether 90 days old or 90 years old, dose timing and patient instruction can be critical to achieving the desired release profile. For pH-dependent coatings like SmartSeal, fluctuation in internal pH needs to be considered when designing the coating thickness and formulation. Internal pH can be affected by whether the medication was taken with or without food, what kind of food, or if the patient is taking other medications which may affect the stomach pH. Design of the coating thickness and formulation should allow pH-dependent coatings like SmartSeal to release at typical and elevated pH levels in the stomach.

Q: If I were developing a new taste-masking project tomorrow, how would I decide which coating is right for my project?
A: That’s an excellent question, and harder to answer than you would think. Several factors go into the decision process for the formulation, including properties of the API, dose level, dosage form, desired release profile, etc, so there is no set answer.

The good news is that Colorcon’s unparalleled Technical Services Group is available to guide customers through the decision process based on their formulation needs, beginning with initial product selection and continuing through development to scale-up and product launch. With access to Colorcon’s technical expertise, our customers can reduce development time and utilise any one of our Technical Service laboratories worldwide for trials, or Colorcon can provide expertise directly at our customers’ sites.

REFERENCES


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Elizabeth Shen has more than a decade of pharmaceutical industry experience, with more than seven years at Colorcon as a Technical Manager focused on film coatings and formulation of solid oral dosage forms. Her experiences range from initial product recommendations to troubleshooting of commercial scale processes resulting in numerous marketed dosage forms.

Dr Shen holds a BS in Chemical Engineering from Case Western Reserve University and went on to complete her MS and PhD from Rutgers the State University of New Jersey’s Department of Chemical and Biochemical Engineering. Dr Shen subsequently completed post-doctoral studies in Rutgers’ Pharmaceutical Engineering Training Program under the direction of Fernando J Muzzio, PhD.
Drug Delivery

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Registration deadline: 24 July 2015
Oral dose development – in particular the inexpensive creation of a simple, once-daily small white pill with optimal therapeutic performance – is the goal of many drug developers. The translation of a drug design concept to the delivered oral dose can be complicated, and understanding the needs of pharmaceutical clients, as well as patients and doctors, is a vital part of the process.

The steps to reach this goal include:
- Creating the target therapeutic profile (TTP)
- Understanding the physicochemical properties of the molecule
- Getting to preclinical and clinical proof-of-concept
- Creating a viable solution for poorly soluble molecules
- Ensuring the stability and robustness of formulations
- Optimising delivery technology and dose forms to get to the TTP
- Meeting the TTP with lowest development cost, fastest development pathway and best therapeutic performance.

Creating the TTP

The TTP is the basic summary of all the required characteristics of a newly formulated drug. Developing this is the first step of the process. There are a number of considerations to bear in mind when creating the TTP, including:
- Indication
- Patient group, e.g. children or adults
- Dosage form
- Size of dose
- Frequency of dose
- Duration of treatment
- Safety profile and adverse reactions
- Mechanism of action
- Clinical efficacy
- Stability at varying levels of temperature or humidity
- Dose profile, or the relationship between pharmacokinetics and pharmacodynamics
- Cost of goods sold (CoGS).

As with many steps in drug development, planning early will improve outcomes and make the process smoother and more cost-efficient. Creating a therapeutic target profile can also help with decision-making processes throughout dose and formulation development, including planning product development strategies, gaining partners and investors, and moving through the regulatory process. Ideally, the TPP should be formulated before initiating Phase I trials, so it can be used as part of the go/no-go decision process.

Understanding the Physicochemical Properties of the Molecule

Understanding the properties of the molecule is critical to developing an ideal oral formulation. The key physicochemical factors are permeability and solubility, which impact the amount and rate of drug absorption, and therefore its bioavailability.2
The US FDA divides drugs into four classes of bioavailability, under its biopharmaceutics classification system:
- Class I – high permeability, high solubility
- Class II – high permeability, low solubility
- Class III – low permeability, high solubility
- Class IV – low permeability, low solubility

The combination of these properties, and the requirements of the TPP, allow the next step of the process to begin, which is creating a formulation for preclinical and early clinical trials.

Catalent has created FormProRx™, a web-based tool that generates suggestions based on API characteristics to help drug developers select the best dose form of oral delivery to improve bioavailability.

GETTING TO PRECLINICAL AND CLINICAL PROOF-OF-CONCEPT

Drug development is a costly business, and getting drugs through studies and to the market as quickly as possible is important to ensure a rapid return on investment, as is ensuring that the drug remains on the market for as long a period as possible without generic competition. Creating an oral formulation can slow the process down, but it is possible to maintain speed by carrying out development steps in parallel.

Formulation steps do not need to be sequential. It is possible to begin preclinical and even clinical trials without a finished formulation by using a bridging study to show bioequivalence between tablets, liquids, or capsules. However, the FDA require 12 months of stability data for a given formulation, so this must be borne in mind when carrying out studies of the final formulation.

Solubility is an important factor in oral drug development to ensure that drugs are absorbed through the gut wall, and it should be considered on a case-by-case basis along with the permeability of the drug (as per the previous section on “understanding the physicochemical properties of the molecule”).

Measurements for solubility and bioavailability include assessing solubility in simulated gastric fluid, and cross-checking this with the drug’s ability to penetrate the gut wall.

Other approaches to improving solubility include changing particle size to increase the surface area. This can be achieved with milling or micronisation, or by dissolving lipophilic drugs in lipids with a surfactant in a self-emulsifying drug delivery system (SEDDS), which creates a drug emulsion on contact with an aqueous environment.

Softgel technologies (Figure 1), such as those developed by RP Scherer, may improve solubility for BCS Class II/IV compounds, and improve solubility and permeability for BCS Class III/IV compounds, and improve dose uniformity and minimise interpatient variability.

Figure 1: A selection of Softgel capsules. Softgel can improve solubility for BCS Class II/IV compounds, improve solubility and permeability for BCS Class III/IV compounds, and improve dose uniformity and minimise interpatient variability.

Figure 2: Hot-melt extrusion creates extrudates – solvent-free solids that can be milled and formulated into a variety of different dosage forms, including controlled delivery and taste-masked tablets.

“It is possible to maintain speed by carrying out development steps in parallel… Formulation steps do not need to be sequential”
pounds. The technology can also improve dose uniformity and minimise variability between patients.

Hot melt extrusion, where drugs are mixed with a polymer and then heated to create a solid solution, improves drug solubility and bioavailability. It creates a solvent-free solid (Figure 2) that can be milled and formulated into a variety of different dosage forms, including controlled delivery and taste-masked tablets. Catalent’s OptiMelt™ hot melt extrusion technology optimises safety and efficacy, and helps speed drugs to market.

ENSURING STABILITY & ROBUSTNESS

The finished oral formulation needs to be physically robust enough to survive packaging, transport and storage. It also needs to be stable, to ensure that the drug’s activity and performance is consistent, whether it is used one month or one year or more after manufacturing. To achieve this, it should have a minimum shelf-life of 18-24 months, with an ideal shelf-life of up to five years. The length of shelf-life is particularly critical for products that have to be shipped over long distances, or that have been developed for rare diseases, where pharmacies may have to stock them for long periods.

The manufacturing process also needs to be robust, and here, simple really is better, both for quality and reliability. The process must be reproducible, so the manufacturer will not face the risk that the finished drug lacks the correct specifications. As with solubility, the processes to improve drug stability will vary on a case-to-case basis. For example, coatings can help to increase the physical stability and robustness of oral tablets and capsules, especially when they are particularly fragile. Coatings applied to tablet or capsule formulations can also control drug release by protecting against degradation as the drug passes through the gut.

OPTIMISING DELIVERY TO GET TO THE TTP

The next step in the process is to optimise the delivery technology and the dose forms, in order to meet the requirements of the TTP. Options include:

- Solution/syrup/elixir
- Suspension
- Powders for reconstitution as suspension
- Dispersible/effervescent tablets
- Chewable tablets
- Orally disintegrating tablets
- Tablets
- Sprinkles, oral powders and granules
- Capsules.

Ideally, the manufacturer will not need to enhance the drug or change its properties to produce the dose form. However, many promising compounds encounter formulation issues. The drug developer or formulation partner must identify the problem in preclinical or early clinical trials and find the right oral formulation solution while meeting as many of the requirements of the TTP as possible.

The following are some examples of the use of the TTP as a development guideline.

Indication

The indication makes a difference in patient-centric dose form choice, particularly in over-the-counter medications. For example, the majority of adult patients prefer pills for indications such as pain, but will ask for liquid medications for coughs and colds.

Whether the disease is common or rare is also significant. For example, if the indication is for a severe and rare disease for which there is no other therapeutic product, the frequency of the dose and the cost per dose may not be as critical as it would be for an antihypertensive, where there is a lot of competition. However, because the drug for the rare disease is not in high demand, the shelf-life may need to be longer.

Patient Group

Different patient groups have different needs. Very young children may be best dosed with liquids, whereas older children may prefer chewables. Middle-aged people may be comfortable with pills, whereas very elderly people may find disintegrating pills easier. There is a wide variety of dose forms designed for the paediatric market, and many of these dose forms can be useful in older people and patients with chronic disorders, who may have issues with taking common oral dose forms such as tablets or capsules. About a third of patients in long-term care, for example, have difficulties swallowing (dysphagia).1

Formulation provides a number of “workarounds”. Parents and caregivers for younger children or frail elderly people may find dosing easier with liquids and fast-dispersing dosage forms (FDDFs), or granules, powders, and sprinkles that can be mixed into foods or drinks. Dosing aids and devices, such as spoons, cups, and calibrated oral syringes, can also help in the administering of drugs to the elderly and children. In contrast, adolescents, adults and the active elderly are more likely to prefer capsules and tablets as these are more convenient and discrete.7

Because paediatric dosing covers such a wide range of ages and sizes, from birth to 18 years of age, formulations for children need to be flexible, so that doses can be titrated according to age and weight. They must also take into account differences in metabolism that may require higher or lower doses. The dose difference between young babies and adolescents could be as much as 50-fold.7

Children under two years old also have differences in gastric pH and gastrointes- tinal motility, which can affect the rate of delivery of controlled-release medications.9

Minttablets or capsules at 1-2 mm are also a good option for children, as their size allows them to be swallowed easily. Liquid drugs are only practical in certain dose sizes, particularly in children, and tablets must be the right size to be swallowed easily. Because the dose is split, this allows titration.8 In a study of children aged six months to six years, 2 mm uncoated tablets were accepted equally as well as sweetened syrups.9

Capsules loaded with pellets or minitablets can also be manufactured at a wider range of dose strengths, or administered using a tablet dispenser. This kind of detailed dose manipulation opens up additional potential indications for oral drugs.

Crushing tablets is not advisable, and tablets to be subdivided must be able to be split in two equal parts.7 Where possible, children’s medications should need to be
administered no more than twice daily.

Taste and smell, and even texture, are all important, particularly for oral drugs for children. Gelatin capsules were introduced in 1834 to mask the taste of drugs, and current approaches include adding flavours, aromas or sweeteners, coating tablets with polymers, liquids or sugars, encapsulation and microencapsulation, granulation, or using taste suppressants and potentiators.10

**Dosing Profile**

For some drugs, variability in the pharmacokinetics and pharmacodynamics has a significant effect on efficacy, safety, and side effects. This can be managed by changing absorption rates, or muting peaks and troughs. Two formulations of a multi-cored tablet, for instance, could allow the same drug to be released at different rates, or in different parts of the body. Gastro-resistant coatings on tablets or capsules will ensure that drugs are carried through the stomach and released in the gut, where absorption rates are often higher.

**THE LOWEST COST OUTCOME FOR THE TPP**

The simplest and least expensive option—and the preferred form for manufacturers—is the plain white pill at a single-dose strength. However, plain white pills may not be particularly patient-centric, especially for those who are taking a number of different medications at different times during the day. A plethora of similar small, white pills could make tablet-taking a complex and confusing process.6

FDA guidelines encourage manufacturers to develop formulations that make it easier for consumers to distinguish one drug from another by colour, shape, or size. Printing or embossing on the surface of the pill may also help.

Different shapes and colours can also improve acceptability and brand recognition, and create a clear differentiation between different brands, or between brands and generics. Nexium® (esomeprazole) is known as a purple pill, for example, and Viagra® (sildenafil citrate) is known as a blue triangular pill. Companies can submit images of shapes, colours, and designs to the FDA as part of the approval process.

**THE IMPACT OF COST**

The cost of drug manufacturing needs to be taken into account in the TTP. For higher-value drugs, where the API is expensive, and for indications where there is little competition, the cost impact of oral dose development is not significant. However, for generic drugs, where costs must be controlled to preserve profit margins, any increase in manufacturing expense is significant, making a plain white pill the most desirable target.

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A significant number of active pharmaceutical ingredients (APIs) are bitter tasting. This bitterness is not an issue in the forms such as capsules and tablets which are swallowed whole. However, many patients are unable to swallow tablets. These include: people suffering from dysphagia with mechanical, neurological or muscular causes; people who are prostrate; and many elderly and paediatric patients.

For these people, where only solid oral dosage forms are available, crushing the tablet is often the only way for them to take their medicine but this is not advisable for various reasons, including safety, and the problem of the unpleasant bitter taste is not easily solved. Studies performed in hospitals have shown that even if these patients crush the drug and add juices, or put the crushed dosage form into food such as fruit compote, this is not enough to mask the bitter taste.

It is therefore necessary to develop alternative oral formulations such as liquids, effervescents and oro-dispersibles.

Formulation of active ingredients in alternative oral forms like these is a challenge, especially for improving patient compliance. Among the various alternative oral forms, rapid-disintegrating / orodispersible delivery systems seem to be attractive for patients. Nevertheless, because of the bad taste of a lot of pharmaceutical molecules, this type of formulation is an issue. Coating appears as a solution for treating these ingredients.

Taste masking chemical systems (sweeteners, flavours) are highly developed, but some of these formulation methods do not work very well (astringency due to the high amount of acid) or complicate the process for preparing tablets. Some require high levels of polyols, which have a laxative effect rendering them unsuitable for repeated administration over long-term treatment.

Sometimes, the quantity of sweeteners and flavourings needed to achieve correct taste masking is such that it does not allow the dosage form development in an orodispersible form because the volume of disintegrating tablet in the mouth is then very large and may contain only 30% or less of active ingredients. Furthermore, the use of sweeteners and flavours complicates and increases the cost of the formulation.

Using organic solvents, these techniques do not always give excellent results in terms of taste masking, and do not fully meet the challenges of formulators (in terms of results and cost optimisation). Conventionally, coating has generally been carried out using techniques such as electrolysis, vapour deposition, and fluidisation. Yet all these methods have limitations including inability to coat small particles due to electrostatic charge build-up, risk of forming explosive vapour phase mixtures when organic solvents are used with air as the fluidising medium, and adverse environmental effects of volatile organic compound (VOC) emissions that require destruction by expensive downstream incineration units.

Clearly, there is a need for environmentally benign and inherently safe coating pro-
cesses. Within the past two decades, supercritical carbon dioxide has been investigated as a benign medium for coating substrates.

The Formulcoat® process consists of a physical masking of each particle and therefore gives excellent taste masking and allows the formulator to work on the usual base of formulation. Formulcoat® does not delay the solubilisation of the API and permits a formulation high in active ingredient, requiring only 5% excipient for some APIs.

The present work reports the design, construction and demonstration of a cGMP pilot-scale CO₂-based coating equipment for pharmaceutical applications. It will present two examples: the first is the coating of pseudoephedrin, a decongestant that shrinks blood vessels in the nasal passages; the second is a taste-masking application on ibuprofen, a non-steroidal anti-inflammatory drug that presents a bitter taste.

Formulcoat®, a novel proprietary, patented supercritical CO₂ process, has several advantages as follows:
- operation at ambient temperatures wherein degradation of the active pharmaceutical ingredient is avoided
- the ability for defining layer thickness of excipient
- coating process without use of organic solvents.

A fluid is in a supercritical area when both temperature and pressure are above its critical values. Supercritical fluids present a density similar to the liquids and are gas-like concerning viscosity. Therefore material and heat transfers are fast and efficient. Properties of these kinds of fluids are easily modified by slightly tuning pressure and/or temperature.

Carbon dioxide is often used because it is a solvent non-toxic, cheap, easily available and its critical point is easy to reach (31°C, 74 bar). Supercritical carbon dioxide is considered a “green” solvent: another important feature is that at room conditions, carbon dioxide is a gas, that means that after process, a simple depressurisation allows to

Figure 1: Carbon dioxide phase diagram.

Figure 2: Schematic view of Formulcoat® process.

Figure 3: The co-injection device, which ensures contact between the native particles and the coating material expanded from the high-pressure vessel.
obtain powder without any residual solvent (Figure 1, previous page).

Supercritical fluids and especially supercritical CO₂ display excellent solute properties for a large range of materials and were found to be helpful to generate solvent-free particles. Briefly, the process involves the dissolution of a 150 bar dense gas into a liquid or a molten fatty solid until its saturation (Figure 2, previous page). The expansion of such a saturated solution or molten phase creates a high super saturation and a sharp temperature decrease leading to particle or droplet formation. API particles then come into contact with the expanded coating agent via designed co-injection device, as shown in Figure 3 (previous page). Due to the high supersaturation generated, fatty agent solidifies onto the particles. The coated particles are then conveyed to a gas/solid separation filter. After expansion, CO₂ becomes gaseous and is easily separated from the processed material.

One specific advantage of Formulcoat® is that the API particles are kept at ambient temperature and therefore are prevented from any degradation. The contact between the native particles and the pulverised fat occurs in a “in house-designed” co-injection device, which further allows the deposition of the coating onto the particles. The native particles are conveyed to the co-injection device by a Venturi system fed by pressurised nitrogen.

Full capacity of the c-GMP pilot-scale unit is 10 kg of coated powder per hour.

Formulcoat® leads to a thin-film deposited onto the particles. The homogeneity and the thickness of the coating layer depend on the nature of the excipient, particularly its filmogenicity. The usual coating agent is Precirol®, a GRAS commercial agent used for taste masking.

Figure 4 presents granulometric properties and SEM pictures of pseudoephedrine before (left) and after (right) Formulcoat® processing using 9% of Precirol®.

We can see that a thin film deposited onto the particles leads to an increase of their average diameters, the minimal thickness of the layer is 3 µm. Particle-size distribution showed a narrow polydispersity for this compound, which was confirmed by microscopy. The process does not alter the particles, neither by attrition nor by agglomeration. For applications in taste masking, a small amount of coated agent is usually chosen (until 10%), in order to maintain immediate release (i.e. avoid sustained release).

Tests were also performed successfully on granulated ibuprofen from Pharmatrans Sanaq AG (Allschwil, Switzerland). Efficient taste masking, checked in a taste-panel session, was obtained with 4% Precirol®. Drug release tests were performed and samples present similar dissolution rates compared with raw materials. Ibuprofen content was verified by HPLC and the homogeneity of the coating was verified by IR-Raman Spectroscopy (Atomic Force Microscope Alpha 300 AR, WITec, Ulm, Germany) and SEM imaging. The coating process is homogeneous and leads to a 6 µm Precirol® film deposited onto the particles (Figure 5).

Powder physical characteristics and ibuprofen dissolution profiles were determined:
- Particle size distribution (D₅₀ = 253 µm)
- Bulk density = 0.459
- Tapped density = 0.515

The USP dissolution profile (pH 7.2) shows a limited slow release effect and met USP dissolution requirement (NLT 80% % ibuprofen release until 60 min). Finally, the coated Formulcoat® ibuprofen has low bitterness and good formulation properties. No agglomeration phenomena occur.

CONCLUSION

To conclude, the supercritical technology presented in this article is a green process for coating formulations, which shows many advantages. This process is mild, without any use of organic solvent, and cost-effective. Furthermore, results obtained by this technology in terms of opportunities to coat small particles efficiently, are often better than those obtained by conventional processes.

The process allows producing kilogram batch scale of coated particles. It could be
achieved in a continuous way, allowing intrinsically high productivity rates. Labile materials can be processed in this way without any degradation. The main application is taste masking of bitter API for orodispersible formulations.

The cGMP qualification of Pierre-Fabre’s new pilot-scale unit is now finished (with a capacity of 10 kg of coated powder per hour) and we are producing GMP batches for bioequivalence studies.

ABOUT THE AUTHOR

Hubert Lochard holds a PhD in Chemical Engineering from Ecole des Mines de Paris, France. He focused his research in the use of supercritical fluid for crystallisation of pharmaceutical compounds.

Then, he joined Pierre Fabre Medicament in order to develop the use of supercritical carbon dioxide in the pharmaceutical field. Dr Lochard is author of dozen publications and patents in this field.
Mir Imran has spent the last 35 years focusing on his passion: creating breakthrough medical innovations that have saved or improved the lives of millions of patients. Mr Imran and his development company, InCube Labs, have a consistent track record of following that theme with many examples of successful companies and products.

Here, Mr Imran speaks with ONdrugDelivery Magazine in detail about one such example, concerned with the oral delivery of peptide therapeutics using a “Robotic Pill” technology, currently under development by Rani Therapeutics.

Q: Oral delivery of proteins and peptides is a notoriously tough market. Over the past decade or so many contenders have come and gone and there is – rightly or wrongly – real scepticism in the industry. What makes Rani Therapeutics’ approach different? What are the key challenges any technology in this market will come up against, and how is Rani’s Robotic Pill different from other oral delivery systems for biologics?

A: Not only over the past decade but over the past four or five decades people have been trying to deliver small peptides and proteins orally. Most notably insulin has been tried multiple times, and other smaller peptides like somatostatin, PTH and others have been attempted by various small, midsize and large companies. One executive at a large pharma recently told us they had counted at least 150 separate attempts over the last 40 years. There have been some minor successes in the sense that for smaller peptides you can achieve low single-digit bioavailability but it is not consistent and there is significant variability between patients and even within individual patients.

So, when we started work on our technology, we decided not to go down the same path that everyone else had gone down and failed. We felt that a better approach would be to take advantage of the biological fact that, unlike the skin, the intestines don’t have sharp-pain receptors. You can poke needles all over the intestine without the patient even being aware of what is going on. The intestines do have stretch receptors so when you have gas you can feel the bloated feeling, even pain, but if a fish bone lodges in your intestine you wouldn’t even feel it.

We took advantage of this physiological fact and decided to create a pill that actually injects the drug in the intestine. As far as the patient is concerned they are taking a pill, but when it reaches the intestine it delivers the drug by injection and the patient is of course oblivious to it. This approach allows us to deliver any biologic of any molecular weight regardless of chemistry and whether it is soluble or not. So not only small peptides and proteins but therapeutic antibodies, for example, and RNAi therapies can easily be delivered by our platform.

In a nutshell, it’s an intestinal injection. It’s taken as a pill and the rest happens automatically. It’s so unique that when we started filing patents there was nothing similar in the existing patent or scientific literature. As a result we have very, very strong patent protection around the technology.

My background is in both engineering and medicine and I’ve been developing engineering-based therapies and medical devices for the last 36 years or so. In the development of Rani Therapeutics’ technology we had to bring together a number of technologies that I’ve been exposed to over the years and a lot of materials science expertise as well.

Q: Are you able to go into more detail about some of the engineering and materials science challenges that you faced during the development of the Robotic Pill?

A: The first hypothesis was to inject the drug into the intestine because there are no pain receptors there. The next question was then about what kind of needle do you use to inject. Immediately I knew we could not have any metal needles, so what do you use? That was a unique challenge. Another challenge: how do you create the force to push the needle into the intestinal wall and how do you inject the drug? Do you have a liquid drug reservoir, for example?

We decided that we didn’t want to have liquid drug, and instead we opted to make the needle out of sugar. It’s an injectable-
grade molecule that’s used as an excipient in injections. We had to do a lot of process development to come up with a sharp needle. Then we had to deliver the drug. A liquid drug would dissolve the needle very quickly, so we decided to put the drug in solid form inside the needle, and that is what we do now.

Rather than delivering and retracting the needle, we made the needle short enough so that it could be delivered and left inside the intestinal wall to dissolve, releasing the drug to be absorbed into the highly vascularised intestinal wall.

The challenge that took us the longest to figure out was developing enough force to deliver the needle into the intestinal wall. Initially I was thinking about using levers and springs but it didn’t make sense that anybody would want to swallow springs every day. It took us almost a year and a half and finally we came up with the idea of a self-inflating balloon. The self-inflation happens when carbon dioxide is produced from a chemical reaction that takes place inside the balloon, and this creates the pressure. It does it in a way that does not stretch the intestines. Once the needles are delivered, all you are left with is a deflated polymer balloon which has the consistency of a bell pepper skin or tomato skin, which the patient can pass out safely.

So while addressing the challenge of creating the force to deliver the needles, we addressed the safety concern that you don’t want to have any solid material remaining that has the potential for causing blockage. We had to stay within the confines of FDA-approved ingestible materials.

We put it all in a capsule and had to develop very robust pH-sensitive coatings so the capsule would not disintegrate in the stomach but would actually go all the way into the intestines, past the duodenum. Once the pH reaches to 6.5 the outer shell dissolves, triggering the chemical reaction inside the balloon which inflates and delivers the needle (see Figure 1).

In addition to safety, we have to achieve high reproducibility – consistent, successful delivery of the needles. In our animal studies we have demonstrated reproducibility of more than 95%. The failures we have noticed are mostly manufacturing process defects that can be overcome with process refinements, better tooling, better machinery and so on. We think that with these refinements we will be able to achieve >99% reproducibility.

Each one of these challenges and solutions I’ve described in a few short sentences took months or even years to figure out and therefore each one of these aspects itself led to a series of patents and IP.

Q: A lot of technology, e.g. electronic tech, is prototyped at a larger size for proof-of-concept and then another challenge is reducing its size down to a viable scale. Was it the case with Rani’s technology that it was initially developed larger and then reduced to the size it is at now?
A: It was developed at the size it currently is, which is about the size of a calcium pill or fish oil capsule that people take every day. We do have plans to downsize it a little bit, but at present it is of a size that most people can take it relatively easily.

Figure 1: As it travels through the GI tract, the capsule remains intact (left), until the pH increases to 6.5/7.0, at which point the capsule dissolves, activating the chemicals within the capsule which react to release CO₂ and begin to inflate the balloon (middle). As the balloon becomes fully inflated, the drug-loaded needles are delivered into the intestinal wall (right).

Q: In short, it appears that this technology completely subverts the problems that excipient-based and other oral protein delivery systems have to face, by taking such a completely different approach...
A: Previous attempts tried to block the proteases and other enzymes which break down proteins but you cannot win the battle with nature. The digestive system is really designed to break down proteins in order to absorb them but if protein drugs are broken down they cease to be drugs and they’re just amino acids. In order to keep the drug in tact you have to prevent exposure to intestinal fluid and so the best option is to quickly inject it without exposing the drug. We’ve done numerous animal studies to demonstrate that this works – insulin and therapeutic antibodies, for example. Because it works without regard to molecular weight, it becomes a ubiquitous delivery platform in that almost any drug can be delivered.

The only limitation of course is how much drug we can put inside the needles. We have a limit of about 3-5 mg per pill and so if you look at the range of therapeutic peptides, proteins and antibodies I think we cover about 70-80% of all biologics out there. Clearly there will be some drugs that are given in the hundreds of milligrams at
a time, and those will not fit into our platform. Every delivery technology has its own limitations. Ours is basically the payload. However many biologics are so potent – in the microgram range in fact, as with PTH, somatostatin, GLP1 analogues, for example – so really it is not a major limitation.

Q: Non-invasive, non-oral delivery routes such as systemic delivery via the lung are advancing and an inhaled insulin product is once again on the market. And advances in the self-injection sector – auto-injectors and wearable injection devices for example – make them more viable products and more tolerable to patients than traditional needles and syringes. How does Rani’s system stack up against delivery technologies that use these other routes of administration?

A: Yes, the auto-injectors have become more user-friendly, the patient doesn’t see the needle and it is a shorter needle. However, you talk to the people who are using these auto-injectors and they hate them. They do it because they have to. Patch based injectors are still injections. As far as inhaled products are concerned, if you are treating a respiratory condition and you can deliver to the lungs then this makes sense and there are many products out there for COPD, asthma and pneumonia. Delivering, for example, insulin via the inhaled route is inherently risky and this is why the FDA has black box warnings on these products; dose variability is an issue and the potential for local interaction with lung tissue. With transdermal delivery, variability can be high depending on where the patient is pressing the patch on their body – a soft area or a bony area. And with microneedles, another big limitation is payload, which is only at microgram level.

That is probably an order of magnitude smaller than Rani’s oral technology. If you have all options available – injection, transdermal inhalation or oral – guess what the patients and the physicians will opt for? And if you talk to physicians who are really interested in patient compliance, they know that efficacy of medications is so dependent on patient compliance – you might have the best drug, but if the patient doesn’t take it, it’s useless.

The Rani route of administration presents specific additional advantages for certain drug molecules, 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 the intestinal route the first organ the drug goes into is the liver. So a drug like the PCSK9 antibody [proprotein convertase subtilisin/kexin type 9 antibody, for reducing low-density lipoprotein (LDL) cholesterol] which Regeneron and Sanofi have, and which Amgen and a few others are developing, is very exciting. We don’t have data yet but it is our belief that because the liver is the first organ the drug goes into after Rani delivery, and because the drug itself is targeting the liver, this could lead to a lower dosage requirement with fewer side-effects because you don’t get drugs stuck in other compartments of the body. For patients not responding to standard statin therapy, PCSK9 can dramatically lower LDL.

One other advantage of the Rani technology, because we have such a unique formulation approach and unique delivery platform, is that we have taken off-patent drugs and put them back to a 20 or 30-year patent life in combination with our platform.

Q: Please could you tell me a little about the company, its founding and key events in its history that have got it to the stage it is at now?

A: I started working on the technology about five years ago. There have been many tough challenges along the way, and it’s the combination of the variety of problems I have solved over the years that really gave me the background to address such a unique set of challenges that we faced in Rani. My background is in electrical and mechanical engineering and materials science, and I went to medical school though never practised medicine. I then started developing companies such as the one which developed an implantable defibrillator which has become the standard of care in cardiology and was acquired by Eli Lilly. I started a number of subsequent companies, mostly focusing on specific therapy areas such as cardiology, CNS and chronic pain etc, and developing devices to treat chronic diseases where we can have a profound impact on patient outcomes. There are some things that can only be treated with – or are better treated with – devices, not drugs.

So this long history of dealing with a number of conditions gave me the back-
ground and familiarity to solve the unique problems Rani is addressing: how do you auto-inject drug into the intestine very cheaply, very reliably and very safely. It’s really a culmination of those decades of experience, making mistakes and learning from them, that has allowed us to do this.

I don’t work alone now. We have a very smart scientific and engineering team, working on the biology, designing the preclinical experiments, and really systematically testing our platform and the drug. This has been led by Dr Mir Hashim [Rani’s Vice-President of Research & Development] who has a PhD in pharmacology and came to us from GSK and is an absolutely brilliant scientist. He’s leading all the preclinical and clinical work. Our engineering team is a very talented group of engineers and materials scientists who are focused on making this platform scalable and manufacturable and reducing the cost. And of course I have a great senior team helping me take Rani and a number of other companies forward.

Rani Therapeutics itself was founded in 2012 and up until then InCube Labs funded its initial development, which took place within InCube. We also manage a venture capital fund called InCube Ventures, which was the first investor. The second round of funding in summer 2013 was led by Google and our venture fund also participated. And then recently we announced a third round of funding where Novartis participated, together with a number of financial investors, and this will raise well over $40 million by the time we’re done.

The Novartis partnership happened at the same time, and it’s a deal we’re very excited about.

We’re in discussions with around a dozen other large pharma companies. You know, they always start off very sceptical because of the long history of failure but I’m quite happy with their scepticism because if they thought it was easy, the technology wouldn’t have as much value. So by the time they go through our technology and examine the data in detail, they realise this might actually work and then they really get very excited about it.

Just imagine three of four players in the market for one particular molecule – basal insulin, for example, or TNF-alpha. Whoever has our platform is going to corner that market – there’s no question in my mind about that, so this could shift market share in key areas dramatically.

“We’ll take our potential partner’s molecule, formulate it into our platform, run animal studies and give them the data. They can then decide whether to sit down and negotiate a licensing deal with us or not. We don’t get into a licensing situation at the outset, without first undertaking the feasibility”

Q: What is the current development and partnership status of the Robotic Pill platform? What are the most interesting applications/product programmes currently being explored?
A: We’re in discussions with numerous companies about delivering their specific molecules. Some of these molecules are already approved, some are in the development pipelines of these companies.

Our approach is that we’ll do an exclusive feasibility study because after they’ve looked at our internal data the next question they will ask is, “Can you actually deliver our molecule?” So we’ve come up with a standardised feasibility test, and during the feasibility period we don’t talk to anybody else and we give an exclusive option to negotiate a licence at the end of the study. During the study, we’ll take our potential partner’s molecule, formulate it into our platform, run preclinical studies and give them the data. They can then decide whether to sit down and negotiate a licensing deal with us or not.

We will likely be announcing a second partnership in the coming months.

Q: The Robotic Pill is showing real promise, has attracted healthy funding and at least one major pharmaceutical partner, and the magnitudes of therapeutic markets that the Robotic Pill has the potential to access are staggering. What is Rani’s strategy for the coming years?
A: We’re very mindful of the regulatory process. The Rani technology is going to be treated by the regulatory agencies as a combination product. The most straightforward and fastest route is to make the first drug we would want to take into humans one that is already approved and has a long history of safety and efficacy. Getting first-in-man experience is a key milestone for us and one which we’re looking forward to. We will also be continuing to focus on forming exclusive licensing partnerships on specific molecules with large pharma companies. And the ultimate for the company if we’re successful could be a public offering at some time in the future.
Our 18 R&D teams in 10 countries are now working on 500+ projects, applying multiple proven and innovative drug delivery technologies to help you deliver optimal release profiles, enhanced bioavailability and better dose forms—preferred by patients and payers.