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# NOVEL ORAL DELIVERY SYSTEMS



ONdrugDelivery Issue N° 77, July 17<sup>TH</sup>, 2017

## NOVEL ORAL DELIVERY SYSTEMS

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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## ADVANCED APPROACHES FOR DELAYED-RELEASE FORMULATIONS

There is growing awareness of the potential for delayed-release formulations to improve patient compliance and increase therapeutic effect. Maria Montero Mirabet, PhD, Senior Project Manager, Drug Delivery Services, and Brigitte Skalsky, PhD, Senior Director, Scientific Communication, both of Evonik Health Care, review advances in delayed-release technology including advances in enteric-coating applications and the use of pulsatile technology to provide tailored lag times.

Delayed-release formulations continue to be a highly relevant formulation approach. Traditionally, the main focuses have been to protect acid-sensitive drugs against gastric fluid and to safeguard gastric mucosa against aggressive actives. In the future, however, targeted drug delivery will be the major motivator for formulating drugs with delayed-release characteristics.

The potential of delayed-release formulations to improve therapeutic effects is reflected in the number of market authorisations in this area, as listed by the US FDA. Although immediate-release (IR) dosage forms strongly dominate the pharmaceutical market, manufacturers increasingly select modified-release approaches to improve their products. New modified-release products, either as extended or delayed release, can lead to better patient compliance or to improved treatment of diseases with specific therapeutic needs.

As an example, rheumatic arthritis (RA) is associated with high cytokines levels, especially in the early morning.<sup>1</sup> Patients with RA can be treated with the glucocorticoid prednisone. This therapy is highly efficient if the drug plasma concentration matches the circadian rhythm of RA patients.<sup>2</sup>

The first commercial product of prednisone was launched several decades

“New modified-release products, either as extended or delayed release, can lead to better patient compliance or to improved treatment of diseases with specific therapeutic needs.”

ago as an IR tablet. Although the drug itself is powerful, when administered in the evening, the IR tablet does not achieve therapeutic plasma concentration to treat the high level of pro-inflammatory cytokine excretion in the early morning. Several scientific communications reported the efficacy of a delayed-release prednisone formulation, targeting the circadian pattern of inflammatory mediators and thus relieving the morning stiffness of rheumatic patients.<sup>3</sup>

However, not until 2012 did the first commercial prednisone delayed-released product gain approval by the FDA (RAYOS® Delayed-Release Tablets; Horizon Pharma, Dublin, Ireland). According to packaging information, RAYOS® releases the active approximately four hours after intake. Administration in the evening therefore leads to an optimal therapeutic plasma level in the early morning hours. As a result, both patient compliance and therapeutic effect have been improved.



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## ENTERIC COATING TECHNOLOGY

Delayed drug release is commonly achieved by the application of an enteric coating on dosage forms such as tablets, capsules and multiparticulates. The main function of an enteric coating is to confer protection. It might be needed to avoid gastric mucosa irritation when exposed to certain drugs, such as non-steroidal, anti-inflammatory drugs (NSAIDs), or to avoid the degradation of acid-sensitive actives, such as enzymes, peptides or proton pump inhibitors (PPIs) in gastric juice. Protection can be easily provided with the application of polymeric coatings, which build films that are insoluble at acidic pH values. For more than 60 years EUDRAGIT® L 30 D-55, a fully synthetic (meth)acrylic copolymer that is soluble above pH 5.5, has been a widely used coating to confer gastric resistance. The reliable functionality of these coatings is reflected by the huge number of marketed drugs formulated with this EUDRAGIT® polymer. Other than cellulosic ethers, EUDRAGIT® polymers are entirely synthetic and thus provide stable product characteristics in narrow specification ranges, reliable processing and defined dissolution characteristics – thereby supporting the QbD approach.

## ENHANCED DRUG RELEASE AFTER STOMACH TRANSIT

In addition to their protective function, enteric coatings are also applied for the local treatment of intestinal diseases. As an example, duodenal peptic ulcers need to be treated locally against *Helicobacter pylori* with antibiotics like clarithromycin and amoxicillin in combination with acid blockers such as cimetidine or ranitidine. Pharmaceuticals for inflammatory bowel diseases, e.g. budesonide, or gastro-intestinal (GI) lavage, e.g. bisacodyl, also use delayed-release coatings implementing EUDRAGIT® L 30 D-55 to target the small intestine.

Focusing on the right absorption site and overcoming drug dissolution or solubility limitations are crucial for the therapeutic effect of certain drugs. Besides that, variations on GI transit times, ionic composition, viscosity and pH of intestinal fluids can have an influence on the *in vivo* performance of drug products.<sup>4</sup> Such variations in gut physiology are not necessarily mimicked by the compendial *in vitro* dissolution test methods.

Still, for most drugs a release within 30 minutes in buffer medium should be fast enough to ensure therapeutic plasma concentrations. However, there are other active pharmaceutical ingredients (APIs) where potential disintegration prolongations of the dosage form *in vivo* may cause discrepancies to the *in vitro* results and consequently an unforeseen reduced response of the medication.<sup>5</sup>

Especially challenging are poorly permeable drugs (BCS III & IV), such as hydroxychloroquine sulphate, atenolol, metforminhydrochloride or furosemide,<sup>6</sup> and poorly water soluble actives (BCS II), such as the NSAIDs ketoprofen, ibuprofen and oxaprozin. Carvedilol (non-cardioselective beta blocker), ketoconazole (antifungal) or fenofibrate (hypercholesterolemia) actives can also be considered in this context.<sup>7</sup>

The solubility of BCS II drugs can vary with the pH range of the small intestine and according to its buffer capacity. As examples, carvedilol and ketoconazole are weak basic drugs ( $pK_a \geq 6$ ) that show a higher solubility at pH values in the duodenum and proximal jejunum. In particular, carvedilol is reported to be mainly absorbed at the duodenum with an important decrease of the amount of drug absorbed from the jejunum.<sup>7</sup> Thus a rapid dissolution in the proximal small intestine can improve its absorption, and hence its bioavailability.

Besides drug properties, gut physiology and its enzymatic activity can influence the stability of certain drugs. The drug efflux transporter p-glycoprotein (P-gp) plays a significant role in limiting cellular uptake.<sup>8</sup> Drugs used in chemotherapy, immunosuppression, hypertension, allergy,

infection and inflammation are substrates of this transporter which goes along with reduced absorption and permeation of the drugs. Examples reported are aldosterone, cortisol, doxorubicin and verapamil.<sup>9</sup> Furthermore, it is reported that the expression of P-gp progressively increases from the proximal to distal region of the intestine.<sup>10</sup> Hence, targeting such drugs to the upper intestine with a rapid onset of action can avoid the exposure to high levels of P-gp and thus enhance bioavailability.

In collaboration with University College London (London, UK), Evonik has developed a novel double-layer technology marketed under the brand name DuoCoat® (Figure 1a). The system can be applied to both monolithic dosage forms and multiparticulates. It consists of two anionic EUDRAGIT® coating layers. The outer layer is a regular EUDRAGIT® L 30 D-55 enteric coating that protects the formulation during gastric transit and starts to dissolve at pH 5.5 by salt formation of the carboxylic acid groups. The inner layer is another enteric EUDRAGIT® L 30 D-55 coating which has been neutralised by the addition of sodium hydroxide. The degree of neutralisation determines the dissolution speed of the coating. The buffer capacity of the neutralised inner layer and thus drug release can be optimised by the addition of organic acids.<sup>5</sup>

When the DuoCoat® formulation enters the duodenum, the environmental pH value increases and at pH 5.5 the outer EUDRAGIT® coating starts to swell and dissolve. Subsequently, intestinal fluid penetrates into the system and reaches the neutralised inner coating layer.

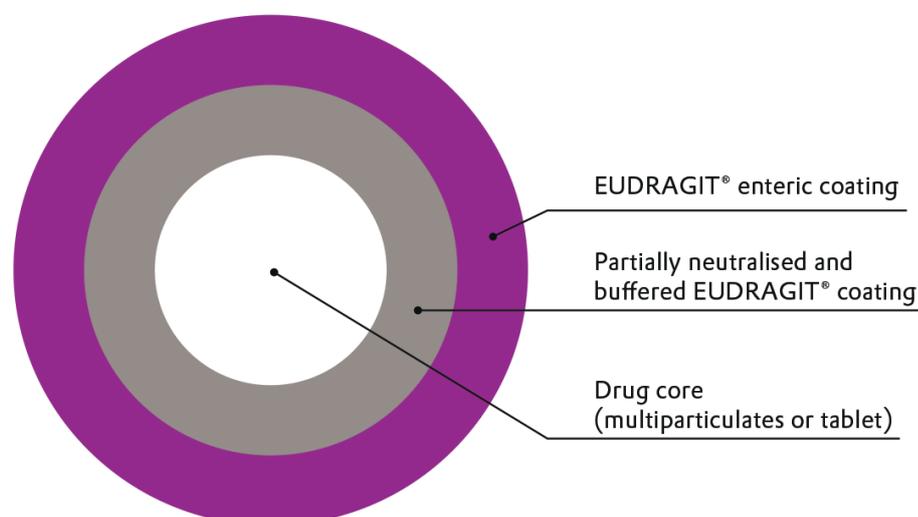


Figure 1a: DuoCoat® formulation design.

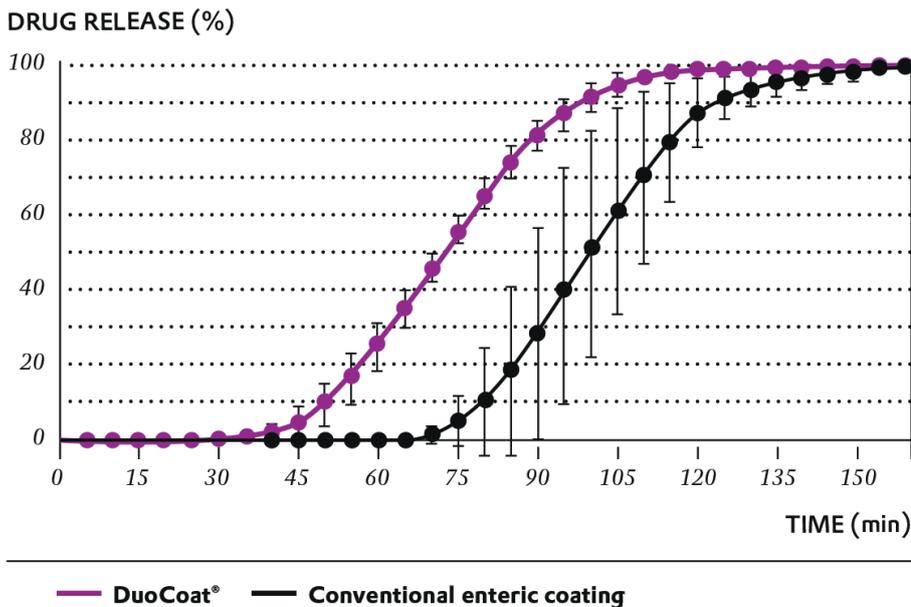


Figure 1b: *In vitro* dissolution profiles (USP II paddle, Hank’s buffer pH 5.6), after two hours in 0.1 N HCl (not shown).

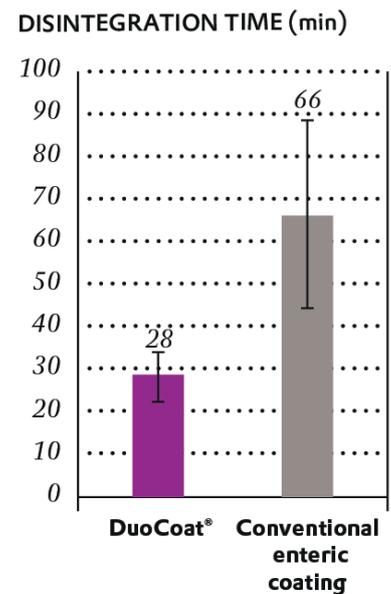


Figure 1c: *In vivo* mean disintegration times of radiolabelled prednisolone formulations (P<0.05).

The inner layer then rapidly dissolves and thus boosts drug release. The accelerated drug release of prednisolone DuoCoat® tablets in comparison with the standard enteric-coated tablets was proven *in vitro* in bio-relevant media<sup>11</sup> (Hank’s buffer pH 5.6) which followed a two-hour incubation period in acidic medium (Figure 1b).

The almost three-times faster disintegration time was confirmed in an *in vivo* study in man (Figure 1c). On average, DuoCoat® tablets disintegrated after 20-35 minutes in the proximal small intestine, and thus were significantly faster than the conventional enteric tablets.<sup>12</sup> By varying the EUDRAGIT® polymer type, specific areas of the GI tract can be targeted with rapid action onset by leveraging the specific dissolution pH values of the polymer used.

### PULSATILE RELEASE WITH TAILORED LAG TIMES

The risk or symptom levels of certain diseases are influenced by the circadian rhythm. Examples are ischaemic heart disease, allergic asthma or arthritis. Medication compliance is often low for such diseases, as night dosing would be required to reduce nocturnal and morning symptoms.

EUDRATEC® MOD, a multiparticulate formulation technology by Evonik, enables high drug plasma levels in the early morning hours while dosing the medication the evening before. Built as a modular system with four different steering tools, pulsatile drug release patterns can be

“The reduction to once-daily dosing confers a major therapeutic benefit for patients who would otherwise need to take medication during the night.”

generated with lag time and slope of the release pattern both tailored to specific therapeutic needs. An inert core is layered with a combination of the API and an organic salt or acid respectively, and then coated with an insoluble but permeable EUDRAGIT® RS/RL layer.

After administration of the formulation and its exposure to GI fluids the permeability of the film coating allows

intestinal fluids to penetrate through the coating and dissolve the organic salt or acid. The resulting anions interact with the cationic polymers and thus increase the permeability of the coating which leads to the intended pulse effect. The thickness and composition of the outer layer control the lag time, whereas the type of organic salt has an impact on the dissolution rate of the drug (Figure 2a).

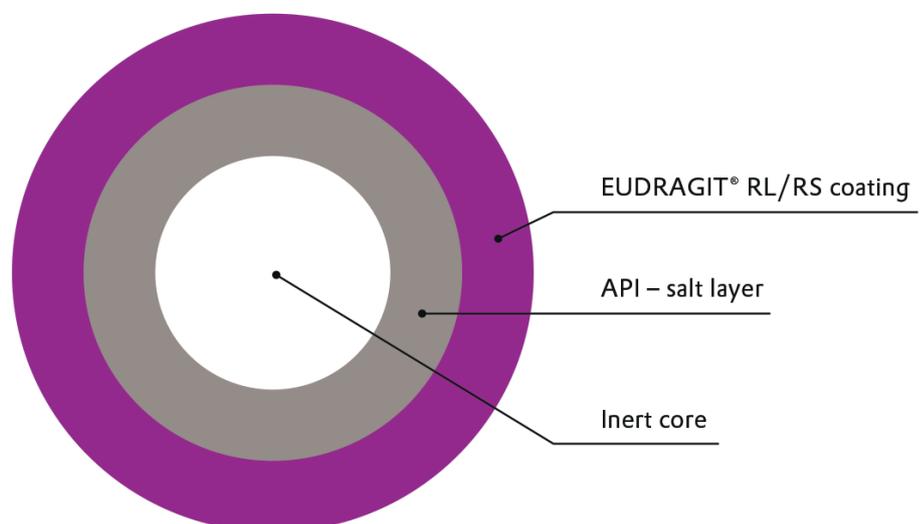


Figure 2a: EUDRATEC® MOD formulation design.

A commercialised example using Evonik's pulsatile technology is Dilzem® (diltiazem hydrochloride prolonged-release hard capsules). Diltiazem hydrochloride is administered to patients who suffer from hypertension and ischaemic heart disease. These patients need a strict medication schedule to reduce morning symptoms and avoid severe health issues. As diltiazem hydrochloride reaches a maximum plasma concentration three to four hours after administration and the risk for severe health issues is highest in the early morning, at least one intake during the night would be required using conventional formulations. Dilzem®, with its pulsatile drug release is able to achieve the highest plasma concentration ( $C_{max}$ ) about 10 hours after dosing (4 hours lag time and 5-6 hours drug release, as shown in Figure 2b) and thus easily provides the therapeutic effect while the patient sleeps. The reduction to once-daily dosing confers a major therapeutic benefit for patients who would otherwise need to take medication during the night.

### ENTERIC FORMULATIONS RESISTANT TO ALCOHOL

Certain patient populations, especially those suffering from strong chronic pain or depression, may tend to consume alcoholic beverages in combination with their medication as a way to cope, contrary to the medical instructions. However, the presence of a hydro-alcoholic solution in the stomach can trigger the dissolution of the delayed-release coating and thus result in "alcohol-induced dose dumping" (ADD). Different from extended-release formulations where ADD might result in high plasma concentrations and thus generate severe side or even lethal effects, with delayed-release formulations ADD consequences are not expected to be as serious. However, loss of the drug effect and hence therapeutic failure, as well as unintended gastric irritation or damage, must be avoided to ensure compliance and successful therapy.

After the Palladone® case received public attention in 2005, the EU EMA and US FDA have provided guidance to avoid alcohol-induced dose dumping of pharmaceuticals. Whereas the EMA regulation is focused on all kinds of modified-release formulations, the FDA has selected individual actives

### MEAN PLASMA CONCENTRATION (ng/mL)

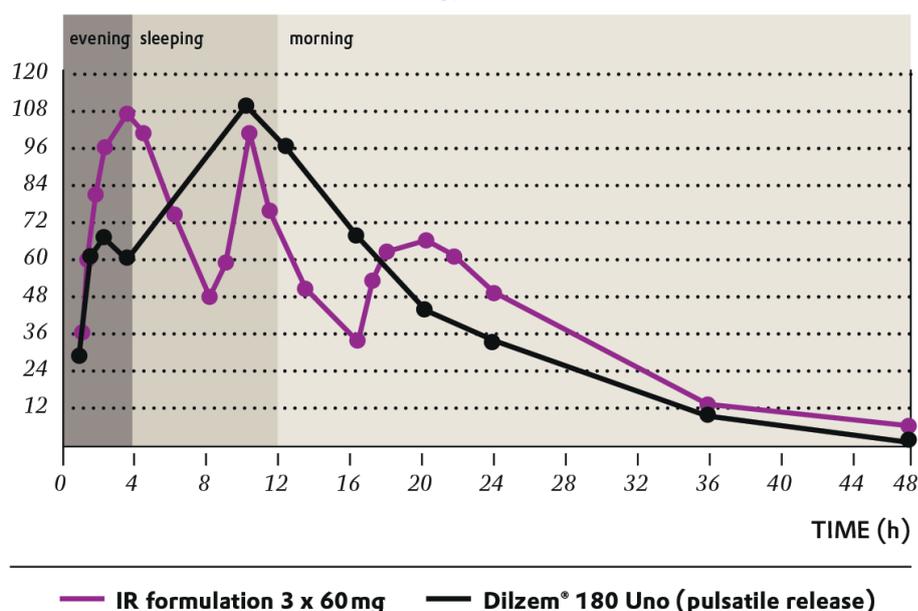


Figure 2b: *In vivo* plasma profiles for Dilzem® 180mg/240mg Uno, product information (Pfizer, 2007).

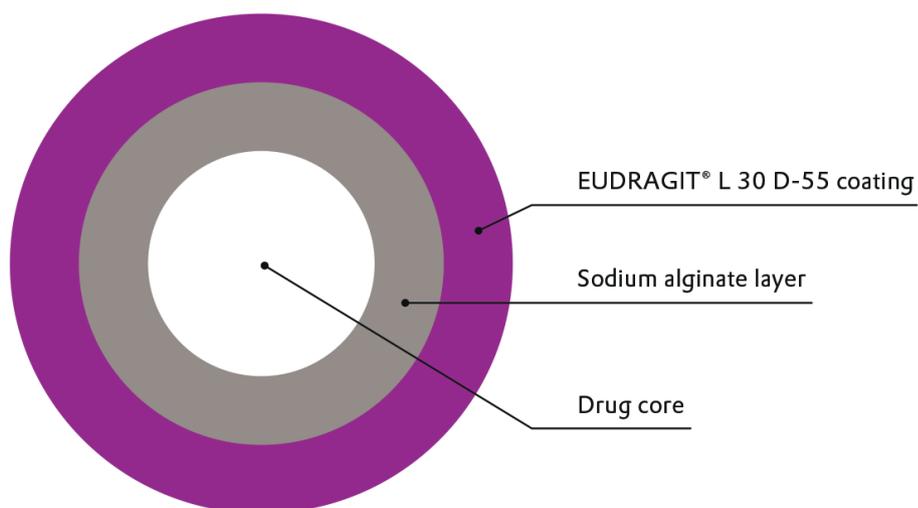


Figure 3a: EUDRATEC® ADD formulation design.

that can become harmful under the ADD effect. Most of these actives are opioids, normally administered as extended-release dosage forms. However, delayed-release products of duloxetine (antidepressive) or dexlansoprazole (PPI) are also required by the FDA to be alcohol deterrent.

EUDRATEC® ADD, a double coating formulation technology, meets the requirements of the FDA regarding ADD. It is capable of generating monolithic and multiparticulate formulations that are resistant to hydro-alcoholic media for over two hours with alcohol concentrations of up to 40%. Multiparticulates are

especially sensitive to ADD because of their higher surface area. EUDRATEC® ADD technology starts from an API core which is coated with a sodium alginate layer, followed by an enteric coating based on EUDRAGIT® L 30 D-55 (Figure 3a). Sodium alginate is a hydrocolloid isolated from marine algae which is soluble in water but insoluble in alcohol. By combining the enteric EUDRAGIT® film with an alginate subcoat the different solubility behaviours of these polymers prevent premature drug release independent from the alcohol concentration (Figure 3b, next page).

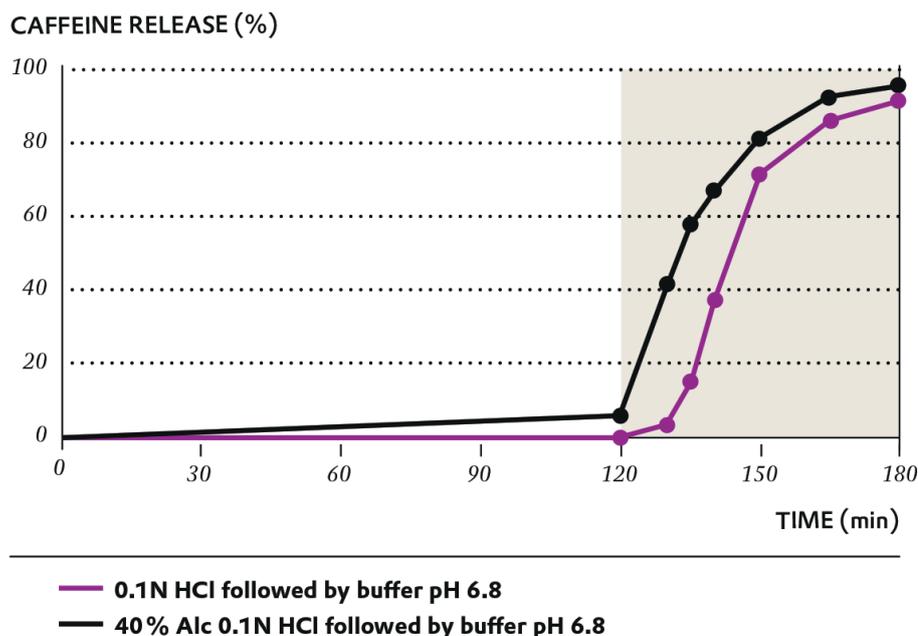


Figure 3b: EUDRATEC® ADD dissolution profiles shown with caffeine pellets.

“Experts can help choose the right excipients for the final application, and professional development services can shorten the way to commercialisation and earlier market launch.”

## CONCLUSION

Overall, the goal and mission of pharmaceutical manufacturers is to produce medicines that offer improved quality of life, fewer hospitalisations and fewer side effects. However, the path to commercialisation is long and challenging. On average it takes at least ten years

from initial discovery to market launch, with average development costs of about \$2.6 billion (£2 billion).<sup>13</sup> Drugs that target the intestinal tract especially need a deeper evaluation of their site-specific bioavailability, stability and safety.

Besides drug properties, unique therapeutic needs such as chronotherapies, or special regulatory requirements need to be considered during development. Hence, intelligent selection of drug delivery approaches become increasingly important. Experts can help choose the right excipients for the final application, and professional development services can shorten the way to commercialisation and earlier market launch.

Evonik, with more than 60 years of experience in the functional applications of EUDRAGIT® polymers, offers its knowledge to support developers and manufacturers and guide them with

formulation development and commercial manufacturing. A partnership with Evonik, either for new developments or for the application of EUDRATEC® technologies can speed up and optimise the road to the market.

## ABOUT THE COMPANY

Evonik, the creative industrial group from Germany, is one of the world leaders in specialty chemicals. Profitable growth and a sustained increase in the value of the company form the heart of Evonik's corporate strategy. Evonik benefits specifically from its innovative prowess and integrated technology platforms. Evonik is active in over 100 countries with more than 34,000 employees. In fiscal 2016 the enterprise generated sales of around €12.7 billion and an operating profit (adjusted EBITDA) of about €2.165 billion. The Nutrition & Care segment is led by Evonik Nutrition & Care GmbH and contributes to fulfilling basic human needs. That includes applications for everyday consumer goods as well as animal nutrition and healthcare. This segment employed about 7,500 employees, and generated sales of around €4.3 billion in 2016.

Evonik's Health Care Business Line serves as a best-in-class strategic partner to the pharmaceutical, medical device and food ingredients industry. The broad product portfolio, deep technical know-how and advanced global capabilities create value by helping our customers reduce risk, enhance quality, improve efficiencies and differentiate their brands. The product and service portfolio includes API contract manufacturing, pharmaceutical excipients, advanced food ingredients, amino acids, cell culture ingredients as well as oral and parenteral drug delivery technologies.

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# 2017/18 EDITORIAL CALENDAR

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Publication Month	Issue Topic	Materials Deadline
Sept 2017	Wearable Injectors	DEADLINE PASSED
Oct 2017	Prefilled Syringes	EXTENDED to Sept 8th
Nov 2017	Pulmonary & Nasal Drug Delivery	Sept 25th
Dec 2017	Connecting Drug Delivery	Oct 23rd
Jan 2018	Ophthalmic Drug Delivery	Nov 20th
Feb 2018	Prefilled Syringes	Dec 22nd
Mar 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Jan 20th
Apr 2018	Pulmonary & Nasal Drug Delivery	Feb 19th
May 2018	Injectable Drug Delivery: Devices Focus	Mar 19th
June 2018	Connecting Drug Delivery	April 23rd
July 2018	Novel Oral Delivery Systems	May 21st

# TECHNOLOGIES & CLINICAL STUDIES FOR THE ORAL DELIVERY OF CALCITONIN

In this piece, Nozer Mehta, PhD, Principal, Peptide Technologies, James P Gilligan, PhD, MSIB, Chief Scientific Officer, Tarsa Therapeutics, and William Stern, PhD, Consultant, Peptide Drug Development, summarise the different technologies that have been in development for oral delivery of peptides through the gastro-intestinal mucosal surfaces via the transcellular or the paracellular pathways and describe the results of several long-term clinical studies on the oral delivery of salmon calcitonin.

## INTRODUCTION

Nearly 95 years after the first unsuccessful attempts to deliver a peptide orally,<sup>1,2</sup> research in this area has resulted in technologies that produce a clinically relevant oral bioavailability of only 1-2% for the majority of peptides studied,<sup>3</sup> despite pharmaceutical and biotechnology companies expending a considerable amount of resources on oral peptide delivery.

With the exception of small peptides such as taltirelin (Ceredist®)<sup>4</sup> and desmopressin (Minirin®)<sup>5</sup> or stable peptides such as cyclosporine (Neoral®),<sup>6</sup> which are commercially available as oral drugs, the majority of macromolecule-based biopharmaceuticals are currently administered parenterally either as intramuscular or subcutaneous injections, or as intravenous infusions, which is clearly less desirable for many patients, especially for chronic indications. Larger stable peptides, such as linaclotide (Linzess®)<sup>7</sup> for irritable bowel syndrome or vancomycin (Vancocin®)<sup>8</sup> and fidaxomicin (Dificid®)<sup>9</sup> for *Clostridium difficile*-associated diarrhoea, are marketed as oral drugs but they are for local gastro-intestinal (GI) targets and are not absorbed systemically.

There are numerous biological barriers that affect the stability, bioavailability and variability of oral peptide delivery. The physicochemical characteristics of the biomolecule may determine whether oral delivery or other non-invasive routes of administration, such as nasal, pulmonary, transdermal, rectal or vaginal delivery, may be more practical, however oral delivery offers the greatest patient acceptance and compliance, hence there is greater emphasis on this route of delivery. The ideal peptide candidate for systemic oral delivery is highly potent, stable,

“An earlier Phase IIa study carried out with the formulation that contained both citric acid and LLC in healthy postmenopausal women showed that LLC increased bioavailability by approximately three-fold.”

resistant to proteases, does not aggregate and has a wide therapeutic window.

## TRANSCELLULAR DELIVERY

Unlike conventional drugs, which are generally lipophilic and are absorbed through enterocytes by partitioning between membrane lipid and an aqueous environment via the transcellular pathway, most naturally occurring peptides have a low log P, a molecular weight greater than 500 and other properties that make them poor candidates for oral delivery via this pathway.<sup>11</sup> In order to utilise the transcellular pathway peptides either need to be lipophilic for passive diffusion, have a receptor on the cell surface for active transport or the presence of a surfactant(s) in close proximity to cells to destabilise their membranes reversibly and allow for peptide diffusion through the cells. Peptide lipophilicity can be increased by reversibly binding them to more hydrophobic molecules, like sodium oleate,<sup>12</sup> or molecules, such as derivatives of caprylic acid, that alter their conformation in such a way as to render them more hydrophobic.<sup>13</sup>



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Receptor-mediated transport can be achieved by attaching a ligand like vitamin B12<sup>14</sup> or biotin<sup>15</sup> to the peptide allowing receptors on the cell surface to transport them through enterocytes. Ideally these ligands are attached via a cleavable linker<sup>16</sup> or the ligand has little effect on the bioactivity of the peptide. For peptides that require a surfactant to enhance transcellular absorption Whitehead and Mitragotri<sup>17</sup> have screened a number of surfactants on Caco-2 cells for their effect on cell viability and transport properties.

One of the most advanced technologies using the transcellular pathway is the Emisphere Eligen<sup>®</sup> technology (Table 1) that uses “peptide carriers” such as caprylic acid derivatives.<sup>13</sup> One such carrier, 5-CNAC (8-(N-2-hydroxy-5-chlorobenzoyl)-amino-caprylic acid), has been used to deliver salmon calcitonin (sCT) orally in a Phase III trial for the treatment of osteoporosis (OP)<sup>18</sup> and in two separate Phase III trials for the treatment of osteoarthritis (OA).<sup>19</sup> 5-CNAC binds non-covalently to sCT. In the acidic pH of the stomach the carrier/peptide complex is insoluble rendering the peptide resistant to degradation. Upon transit to the duodenum, where the pH rises to 5.5 or greater, the complex is soluble and the peptide is absorbed through the epithelial membrane into systemic circulation.<sup>20</sup>

## PARACELLULAR DELIVERY

Peptides that cannot be transported by the transcellular pathway are absorbed via the paracellular route, which involves peptide transport through tight junctions also known as *zona occludens* between epithelial cells in the GI tract. Tight junctions are maintained by a group of proteins that include cadherins, claudins, occludin and junctional adhesion molecules, which seal together adjacent cells and provide cytoskeletal anchorage.<sup>21</sup>

Several technologies have been developed to open tight junctions transiently and allow passage of peptides into the systemic circulation, all in

“Different meta-analyses, including one conducted by the FDA, have indicated that there is little evidence of a causative relationship between calcitonin and cancer. ... Following a full review by the FDA no black box or bolded warning was issued for sCT products nor was a limitation on the duration of use imposed, as is seen with other drugs used in the treatment of OP.”

various stages of preclinical or clinical development. The leading technologies for paracellular transport are:

- POD<sup>™</sup> technology (Oramed Pharmaceuticals, Inc, Jerusalem, Israel)<sup>22</sup>
- TPE<sup>®</sup> technology (Chiasma, Inc, Waltham, MA, US)<sup>23</sup>
- GIPET<sup>®</sup> technology, which may also work partly by a transcellular mechanism<sup>24</sup> (Merrion Pharmaceuticals, Dublin, Ireland (in administration))
- Access<sup>™</sup> delivery system (Proxima Concept, Ltd, St Helier, Jersey, UK)<sup>25</sup>
- Peptelligence<sup>™</sup> technology (Enteris BioPharma, Inc, Boonton, NJ, US).<sup>26</sup>

In order to enhance paracellular transport these technologies utilise a variety of permeation enhancers that are generally non-ionic surfactants, acyl carnitines, fatty acids, fatty acid esters, bile salts and alkyl glucosides.<sup>17</sup> Other chemicals that have been found to enhance paracellular transport include calcium chelating agents,<sup>27</sup> sodium salicylate,<sup>28</sup> aspirin,<sup>29</sup> non-steroidal anti-inflammatory drugs (NSAIDs),<sup>30</sup> phenothiazines<sup>31</sup> and chitosan.<sup>32</sup>

The Peptelligence<sup>™</sup> technology has been used successfully to deliver sCT orally in Phase II<sup>33</sup> and Phase III<sup>34</sup> trials. The technology employs an enteric-coated tablet that contains citric acid and in certain embodiments lauroyl-L-carnitine (LLC), an acylcarnitine (Table 1). The enteric coating protects the peptide from degradation in

the stomach and allows the tablet to release its contents in the intestine. Citric acid enhances peptide absorption by lowering intestinal pH to inhibit proteolytic activity and also chelates intracellular calcium, while the acylcarnitine enlarges the pore size of tight junctions thus increasing their hydrodynamic radius.

## LATE-STAGE ORAL DELIVERY STUDIES WITH sCT

Salmon calcitonin (sCT) is a 32 amino acid peptide hormone that inhibits osteoclasts and induces the suppression of degradation of collagen type II, the primary protein in cartilage.<sup>10</sup> Here follows a summary of clinical trials of various oral formulations of sCT, including Phase II studies in patients with osteopenia, Phase III studies in postmenopausal OP and Phase III studies in men and women with osteoarthritis (OA) of the knee. These studies were performed using two of the leading oral delivery technologies, namely the Eligen<sup>®</sup> technology for transcellular transport and the Peptelligence<sup>™</sup> technology for paracellular transport (see Table 1).

### Studies with the Transcellular Eligen<sup>®</sup> Technology

Several companies and research groups have attempted to develop oral delivery technologies for sCT.<sup>35</sup> The Eligen<sup>®</sup> technology<sup>13,36</sup> utilises carriers that bind non-covalently to a peptide and increase

Company	Technology	Permeation Enhancers	Permeation Route	Indication	Development Stage
Emisphere	Eligen <sup>®</sup>	5-CNAC	Transcellular	Osteoporosis Osteoarthritis	Phase III
Enteris/Tarsa	Peptelligence <sup>™</sup>	Citric acid, LLC	Paracellular	Osteopenia Osteoporosis	Phase II Phase III

Table 1: Transcellular and paracellular delivery technologies employed in late-stage studies for oral delivery of salmon calcitonin.

its lipophilicity. This technology has been used for the oral delivery of several peptides, and a currently approved product for the oral delivery of vitamin B12.<sup>37</sup> 5-CNAC has been extensively studied in combination with sCT in clinical studies to determine bioavailability, efficacy, food effects, and interaction with water intake.<sup>38,39</sup> A Phase II study in postmenopausal women demonstrated significant reductions in bone resorption as assessed by serum CTX-1, a marker for bone resorption, over three months.<sup>40</sup>

These early clinical studies were followed by a large randomised, double-blind, multicentre, placebo-controlled Phase III study to evaluate the efficacy and safety of this formulation in the treatment of OP in postmenopausal women taking calcium and vitamin D.<sup>18</sup> In this three-year study a total of 4665 subjects were randomised into either the treatment or placebo group. Subjects were instructed to take a single oral tablet containing 0.8 mg sCT once daily in the evening 30-60 min before dinner, together with a maximum of 50 mL of water.

There was a significant decrease in CTX-1 in the treatment group compared with placebo, similar to what was seen in the earlier Phase II study. The primary endpoint required a reduction in new vertebral fractures however, and there was no significant difference in the incidence of new vertebral fractures between the treatment and placebo groups. The mean increase in bone mineral density (BMD) at the lumbar spine (LS) in the treatment group was 1.02%, which was significantly higher, by 0.83%, than the placebo group.

The authors of the study believe that the primary reason for lack of significant anti-fracture efficacy was the lower than expected blood exposure  $C_{max}$  of sCT of 28 pg/mL and 22 pg/mL at the beginning and end of the study respectively, which was at least four times lower than seen in the earlier Phase I and Phase II studies. The authors suggested that there was a technical failure of the formulation that led to the lower than expected exposure to the drug.

With regard to safety, the study medication was generally well tolerated, though there were higher incidences of GI disorders and vascular disorders in the treatment group compared with placebo. Importantly, in light of the potential safety issue of sCT discussed later, no differences in cancer events were observed between the two groups.

Two Phase III studies were also carried out with oral sCT for the treatment of knee OA using the 5-CNAC enhancer.<sup>19</sup> In these two double-blind, randomised, placebo-controlled, multicentre studies, 0.8 mg sCT or matching placebo was given twice daily for 24 months. Approximately 1200 patients were randomised in each of the two studies and divided equally between the treatment and placebo arms. The primary endpoints were the change in joint space width (JSW) over 24 months in the signal knee measured by X-ray, compared with placebo, and also change in pain and function using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire.

Neither of the studies demonstrated a significant treatment effect of change in JSW at intervals during the study or at the 24-month study endpoint. The WOMAC questionnaire scores at the 24-month endpoint demonstrated a treatment effect in one of the two studies but the effect was considered non-significant due to the hierarchical testing procedure.

In this study as well, there was a four-fold decrease in sCT exposure compared with the earlier phase studies at comparable doses, and the authors suggest that the Phase III failure is the result of a flawed hypothesis and a technical failure of the oral formulation that might have occurred as a scale-up issue in the manufacture of the tablets.

#### Studies with the Paracellular Peptelligence™ Technology

Tarsa Therapeutics has carried out a 48-week Phase III study for the use of

oral sCT in the treatment of OP, and a Phase II study for the treatment of postmenopausal women with osteopenia using its Peptelligence™ technology. It should be noted that, although these studies utilised the components of the technology previously described, they did not include LLC as one of the active excipients. The Phase III OP study (ORACAL) was a randomised, double-blind, double-dummy, active- and placebo-controlled, multiple-dose study, enrolling 565 postmenopausal osteoporotic women to assess the efficacy and safety of oral recombinant calcitonin.<sup>34</sup>

The primary endpoint of the study was to determine the increase in LS BMD following treatments compared with baseline and Miacalcin (sCT) nasal spray. Oral treatments were with identical appearing tablets containing either 200 µg (1200 IU) of sCT or placebo, and nasal spray treatments contained 33 µg (200 IU) sCT.

The study met its primary endpoint and it was concluded that orally administered sCT resulted in improvement in LS BMD that was superior to that obtained with commercial nasal sCT spray or placebo after 48 weeks of treatment, with significant improvement in LS BMD observed after six months of treatment (Figure 1).

Few women in any group reported any serious adverse events (AEs), and overall the safety findings were not dissimilar in the different treatment groups, although the women in the oral group did report greater incidences of nausea and dyspepsia, a side effect that has also been reported for women receiving injectable sCT. Interestingly there was a significantly

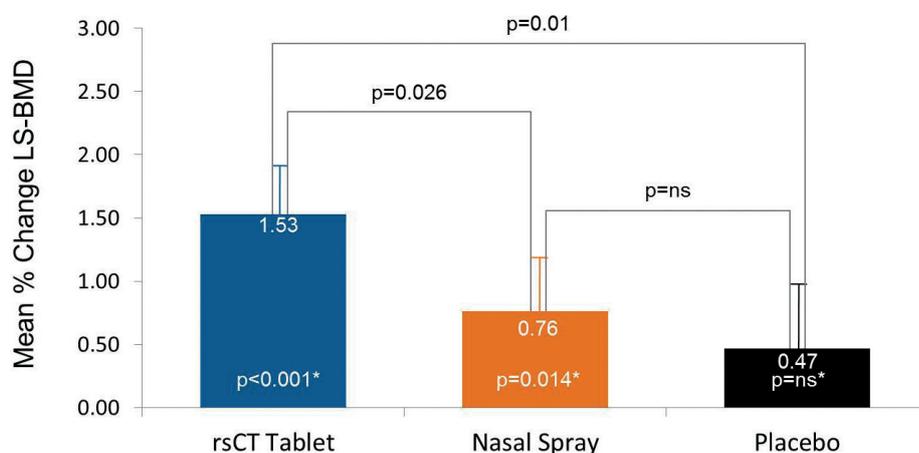


Figure 1: Increase in lumbar spine BMD in osteoporotic patients\* at one year following treatment with oral sCT, compared with nasal sCT or placebo, utilising the Peptelligence™ technology. Oral sCT was superior to nasal CT and placebo at primary endpoint.

\* Compared with baseline. Modified intention to treat population, last observation carried forward.

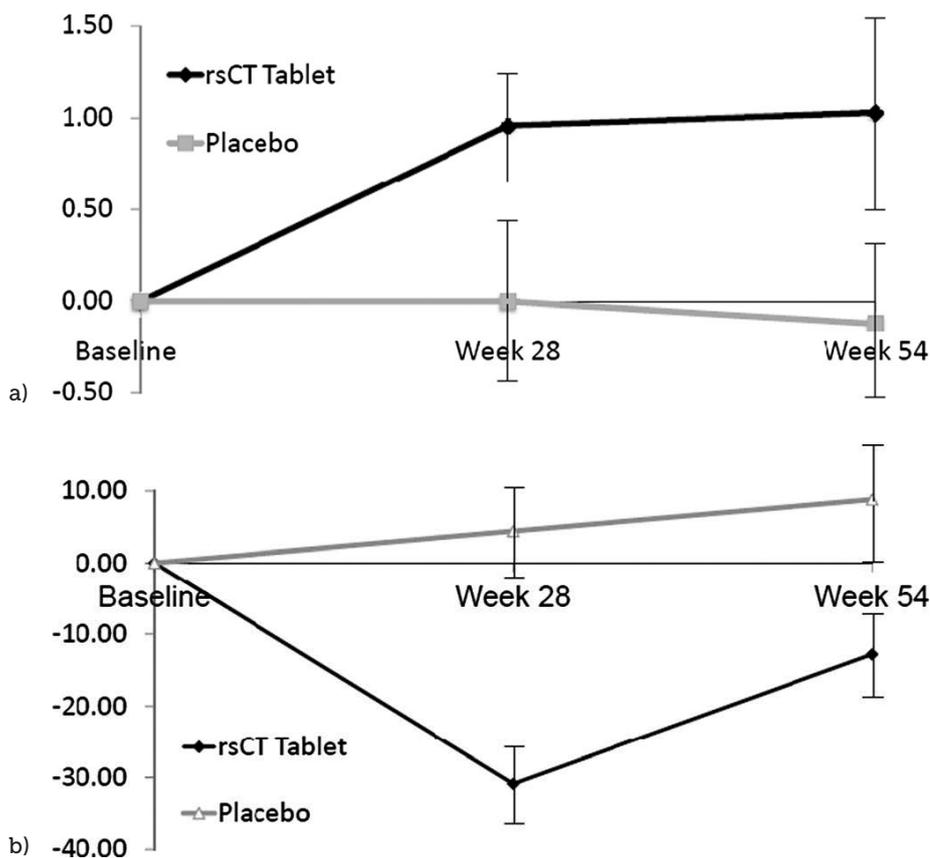


Figure 2: Mean percent change in A) lumbar spine BMD and B) CTX-1 over time in women with osteopenia following treatment with oral sCT utilising the Peptelligence™ technology.

Reprinted from: Binkley N, Bone H, Gilligan JP, Krause DS, "Efficacy and safety of oral recombinant calcitonin tablets in postmenopausal women with low bone mass and increased fracture risk: a randomized, placebo-controlled trial". *Osteoporos Int*, 2014, Vol 25, pp 2649-2656.

reduced (approximately five-fold lower) immune response in subjects receiving oral sCT compared with nasal sCT. Based on the data from this study a NDA has been filed with and accepted by the US FDA.<sup>41</sup>

The Phase II study was conducted to investigate the effect of oral sCT on BMD of the spine in postmenopausal women with low bone mass and at increased risk of fracture, but who did not meet the BMD criteria for OP.<sup>42</sup> A total of 129 women were randomised between oral sCT and placebo and treated with a daily tablet for 54 weeks.

The study results demonstrated an increase in LS BMD, a reduced bone

resorption marker CTX-1 and a reduced total proximal femur BMD loss in women taking oral sCT (Figure 2). Few women in either group experienced serious AEs, although mild GI AEs were common in both groups and resolved upon discontinuation. This study also demonstrated a lack of a food effect for this formulation.

## DISCUSSION

It appears that the Eligen® formulations based on 5-CNAC may have encountered a problem when scaling up the tablet manufacturing for the large Phase III studies, since the  $C_{max}$  values were 4-5 times

lower than expected from the early phase studies. With the lower exposure there was no-reduction in vertebral fractures. However, there was some evidence of efficacy with regards to the secondary measures that may respond to lower exposure to sCT. In the OP study there was a small but significant increase in LS BMD and significant reductions in the markers for bone resorption urinary CTX-I and CTX-II. Similarly in the two OA studies there was some effect on pain, stiffness, function and a small decrease in the marker for cartilage degradation.

The studies carried out with the Peptelligence™ technology for OP and osteopenia both demonstrated a highly significant increase in LS BMD and a reduction in the primary marker for bone resorption, serum CTX-1, and this should translate into preservation of bone density in osteoporotic and osteopenic women.

A direct correlation with reduction in vertebral fractures cannot be made since these studies were not designed or powered to measure fracture prevention efficacy. However, the data suggest that 200 µg tablets of oral calcitonin may provide more consistent and greater exposure to calcitonin than the currently marketed nasal calcitonin formulations, which could translate to reduced fracture risk.

As previously mentioned, the Peptelligence™ formulation used in these studies did not include the active excipient LLC and no PK measurements were performed. However, an earlier Phase IIa study carried out with the formulation that contained both citric acid and LLC in healthy postmenopausal women showed that LLC increased bioavailability by approximately three-fold.<sup>33</sup>

Salmon calcitonin has been marketed for over 30 years as injectable and nasal formulations. In 2012, following a meta-analysis of a variety of clinical studies and marketing data, the EMA suspended calcitonin nasal spray from the market and limited the duration of use of other calcitonin products due to a putative association with cancer.<sup>43</sup>

However, different meta-analyses, including one conducted by the FDA, have indicated that there is little evidence of a causative relationship between calcitonin and cancer.<sup>44,45</sup> The combined safety data from the two one-year clinical trials with the Peptelligence™ oral sCT formulation demonstrated no signal of carcinogenicity,<sup>46</sup>

"The data from the studies described here hold out the promise that an oral formulation of sCT will eventually be approved for bone disorders such as OP or as a potential disease modifying drug for the treatment of OA,<sup>47</sup> which is a large unmet medical need."

nor did the three long-term studies with the Eligen® oral sCT formulation.<sup>18,19</sup> Following a full review by the FDA no black box or bolded warning was issued for sCT products nor was a limitation on the duration of use imposed, as is seen with other drugs used in the treatment of OP (Forteo®, TYMLOS™, and all bisphosphonates).

There are many real world issues that should be taken into consideration when developing an oral formulation targeted to support commercial needs. The ruggedness of the manufacturing process, the cost of goods of the peptide needed for a low single-digit bioavailability formulation, the effect of food and water intake on the efficacy of the formulation and the effect of concurrent use of proton pump inhibitors or other medications are all variables that will impact the efficacy of the drug in chronic use and need to be evaluated.

Dosing flexibility is particularly important for chronic therapies, and the formulation needs to be “rugged” enough to allow for variabilities in patient compliance, particularly with elderly populations.

The long-term room temperature stability of the tablet formulation is also a consideration since it will avoid the need for cold chain transport and patient refrigeration of the tablets, and will enable sampling by sales representatives.

The data from the studies described

here hold out the promise that an oral formulation of sCT will eventually be approved for bone disorders such as OP or as a potential disease modifying drug (DMOAD) for the treatment of OA,<sup>47</sup> which is a large unmet medical need. Also based on the evidence from the OA studies that there was efficacy in the pain scores and a decrease in cartilage markers, an appropriate oral sCT formulation could also be developed for pain and mobility in patients with knee OA.

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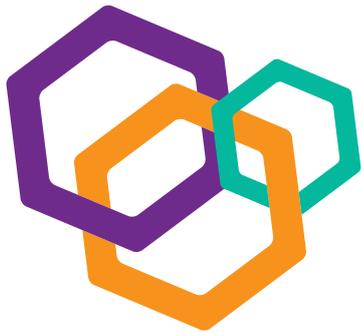
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## THE PRESCRIPTION ABUSE EPIDEMIC: DESIGNING A SOLUTION

Aia Malik, Product Manager, Healthcare, and Gemma Budd, Director of Technology and Strategy, both of Lucideon, discuss the journey behind Lucideon's proprietary iCRT-deter technology, reviewing the escalating prescription abuse problem, abuse deterrent formulation (ADF) drivers and the factors that will shape the future of the iCRT-deter technology, which provides tamper-proofing and enhanced safety of pharmaceuticals. It has been used to give abuse-deterrent features to formulations of opioids and highly potent compounds.

Addictive compounds such as Hydrocodone and Oxycodone, both opioids, are regularly prescribed for the treatment of acute and chronic pain. Opioids work by tempering the perception of pain by the body. However they also boost dopamine levels in particular areas of the brain, resulting in euphoric feelings that may lead to addiction. Extended release formulations can contain up to three times the dose of immediate release products leading some abusers to try to extract the entire available drug to amplify this euphoric effect.

With the extensive effects that abuse can incur, from impacting the nervous and cardiovascular systems to the economic costs, it's unsurprising that the abuse of these compounds has drawn the attention of regulatory and governmental bodies. For manufacturers, reducing the risk of abuse associated with certain compounds has become both a regulatory and ethical issue.

### TACKLING THE PROBLEM

Prescription drug abuse is currently considered an epidemic by the US Centers for Disease Control and Prevention (CDC). The levels of abuse, particularly in the case of opioids, are a key area of concern for public health, governmental and regulatory bodies such as the US FDA. Accordingly, vast investment in national programmes has been made to try and tackle the problem.

One such programme is the Prescription Drug Abuse Action Plan, which includes accelerating priority New Drug Application reviews by the FDA to develop analgesics

with no abuse potential and abuse-deterrent formulations (ADF) of opioid medications and other drugs with abuse potential.

The FDA has been encouraging the development of opioid formulations with abuse-deterrent properties and has made clear that new and existing opioid medications should be made less susceptible to abuse. In support of this it has published two key guidance documents entitled *Abuse-Deterrent Opioids Evaluation and Labeling* and *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*. The documents offer guidance on how to prove abuse deterrence of opioid formulations and outline some key categories for abuse-deterrent features.

While regulatory pressures have helped form an emerging market for abuse-deterrent (or tamper-proof) technologies, other major drivers that have influenced the rapid uptake of such technologies include:

- Patents and generics development
- Corporate social responsibility
- Competitive advantage and differentiation
- Future-proofing of products.

More recently, the FDA surprisingly requested the withdrawal of one of the established supplies of oxymorphone, citing the risk of abuse as being the major cause. This was unexpected as it was thought that protecting the patients' supply of important medication outweighed reducing the abuse risk. This action further increases pressure on manufacturers to



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respond to this issue immediately and opens the door for new entrants.

## ROUTES OF ABUSE

There are several known routes for abusing prescription drugs. These include:

- Intravenous intake
- Chemical tampering or crushing, followed by insufflation
- Oral abuse (ingesting a number of whole tablets greater than the prescribed dose).

To address these problems the FDA released a final guidance document highlighting several general formulation strategies that can be adopted to permit abuse deterrence marketing:

1. Physical/chemical barriers – e.g. preventing chewing, crushing, or grinding (physical).
2. Agonist/antagonist combinations.
3. Aversion – e.g. adding of nasal irritants to deter intranasal abuse, or unpleasant tasting chemicals released on crushing.
4. Delivery system – a drug release design or method of drug delivery that can offer resistance to abuse.
5. New molecular entities and prodrugs – a formulation that is activated by enzymatic activity in the body's metabolic process.
6. Combination – two or more of the strategies.
7. 1-5, in conjunction for abuse deterrent effects.
8. Novel approaches – new methods not covered in strategies 1-5.

## DESIGNING A USABLE PRODUCT

Through our research we gained some critical insights from manufacturers and practitioners about concerns around tamper-resistant and abuse-deterrent products or technologies. Of those the biggest issue was usability for non-abusing patients, which consequently impacts compliance. As such our technology, iCRT-deter, had to be designed to factor in the following:

- Usability for regular use
- Small, easy to swallow tablets (consider geriatric/paediatric population)
- Crushing may be required for administration
- Compatibility with other technologies
- Ease of processing/formulation
- Versatility to accommodate other delivery routes, e.g. oral, sublingual.

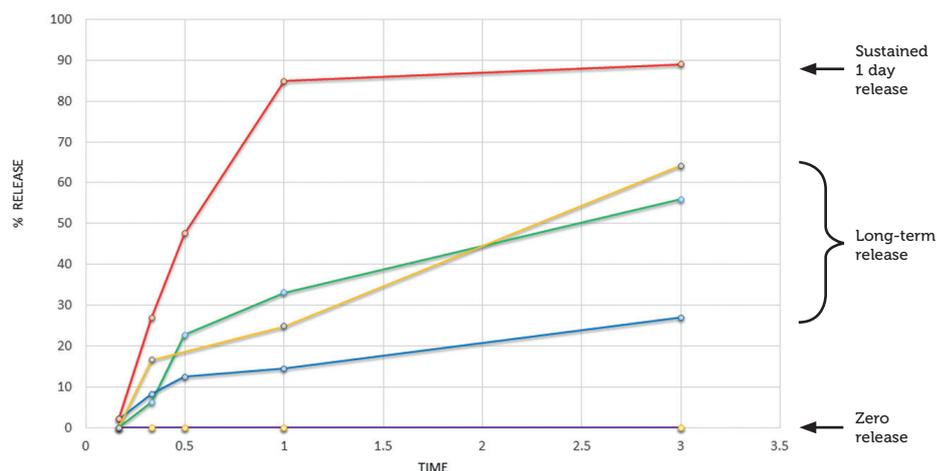


Figure 1: A range of release profiles controlled by rate of carrier dissolution.

## INTRODUCING iCRT-DETER

Lucideon's iCRT-deter technology is a smart carrier that has been designed to give critical abuse-deterrent features to addictive or high dose formulations, without compromising ease-of-use for, and thus compliance of, non-abusing patients. In addition to being a controlled release technology that aims to boost compliance, the carrier has tamper-resistant features built in to tackle three key routes of abuse:

- Crushing in order to snort
- Dissolving in order to inject
- Extraction in order to access the raw drug.

### Key Features

At its core Lucideon's iCRT-deter is a controlled-release platform. The technology incorporates active molecules within its nano-porous silica matrix, offering superior, adaptable release profiles. The technology also utilises a range of triggers such as time, pH and moisture to achieve more specific drug delivery profiles, such as pulsatile and delayed release.

The platform was designed to tackle difficult molecules and uses inorganic materials, such as silica, to avoid common issues caused by polymeric carriers and excipients. These problems can include unpredictable drug release and swelling/absorptive behaviours, and unwanted degradation products, which can impact the active pharmaceutical ingredient (API) stability and affect local tissues.

The platform has also been tailored for injectable dose forms and is being developed to address critical issues such as large molecule instability and bioavailability challenges for poorly soluble compounds. Its powder form makes it ideal for incorporation into, and enhancement

of, existing formulation technologies – essentially replacing the API powder with the iCRT powder.

There is a range of release profiles (Figure 1):

- **Immediate release** – employing triggers such as pH or moisture
- **Delayed release** – using coatings or triggers
- **Extended release** – hours to weeks depending on the dose form and profile required
- **Bi-phasic release** – various rates of release for one compound or combining different compounds that have different optimal release requirements.

## KEY FEATURES OF THE TECHNOLOGY

No single technology will completely prevent abuse, but a benefit of Lucideon's technology is its versatility and relative simplicity – it can be readily combined with other ADF technologies. It is intrinsically a controlled-release technology as well as being abuse deterrent, so this dual benefit is appealing from both a manufacturing and end-user perspective.

The abuse-deterrent drugs on the market offer aversion features, physicochemical barriers such as gelling when crushed or immersed in water or crush resistance. iCRT-deter offers a combination of strategies including resistance to crushing or manipulation via solvent extraction to avert insufflation or intravenous abuse. It can also protect patients from unintentional misuse through parallel alcohol consumption. Alcohol-induced dose dumping not only affects clinical efficacy, but also poses a major safety risk for modified-release products in general that can dose dump in the presence of alcohol, resulting in increased exposure.

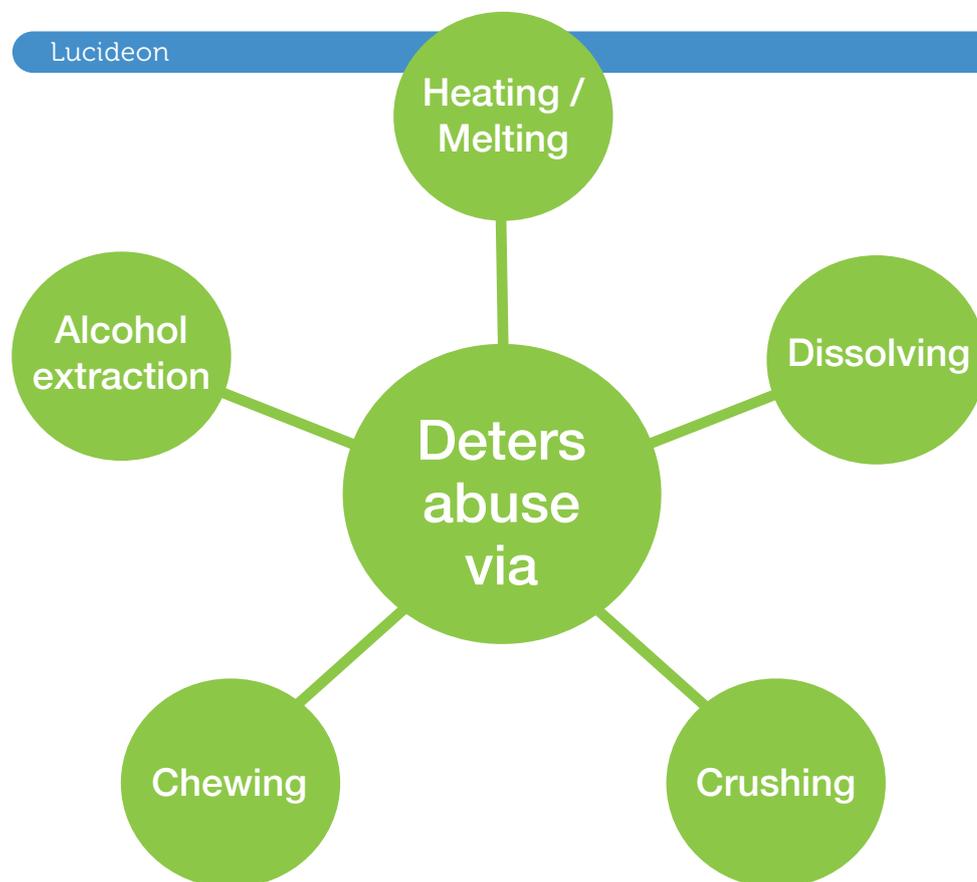


Figure 2: The key abuse deterrent features of iCRT-deter.

The key abuse deterrent features of iCRT-deter include (Figure 2):

- **Solvent extraction** – Equal or significantly reduced drug dissolution in alcoholic media and other household solvents as a result of its tuneable surface chemistry, charge and microstructure.
- **Crushing** – The material used is an extremely hard inorganic structure which is very hard to crush beyond its primary particle size without specialist grinding equipment. Importantly the control of release is dictated by the powder – not the tablet – so crushing back down to powder does not significantly accelerate the drug dissolution. This outperforms other “crush-resistant” tablets – often significantly larger than normal – that compromise the ability for normal patients to take the drug, resulting in reduced compliance and reluctance to prescribe.
- **Heating** – The carrier has a very high melting point (1000°C+), which deters injection because melting the carrier will destroy the drug. Furthermore, heating the carrier will densify the nanoporous network, further trapping the drug within the powder.
- **For injection** – Lack of powder solubility, relatively large, angular particles and poor flow properties make it unsuitable for injection through suspension – it clogs up even large gauge needles.

- **For insufflation or oral abuse** – Recalling that the control of drug release is dictated by the powder, not the tablet, snorting the drug-loaded powder will not result in a “hit”, and most of the drug will be cleared by the body before it is able to release from the carrier.

Further, as the technology results in a one powder material with built in abuse-deterrent features, it can be easily combined with other deterrents. Colour leaching in liquids can be employed to deter spiking of drinks and antagonists that only release on manipulation can be added, as is currently used in some marketed opioids. As the technology can be used to give abuse-deterrent features to the active ingredient selectively, the products can be readily combined with antagonists whilst still allowing them to perform as required.

#### OTHER DRUG USES

Although opioids have taken centre stage in the development of the technologies, a market is emerging for the abuse deterrence of other potent and addictive drugs, mainly from Schedule II controlled substances, such as prescription amphetamines. Anti-depressants, sleeping aids and Attention Deficit Hyperactivity Disorder (ADHD) treatments all have high abuse potential. To future-proof products and gain larger market share,

some companies are already employing ADF strategies for these compounds. It is inevitable that more will follow.

iCRT-deter has been developed as a platform technology so that it can be applied to other compounds. As most of the abuse-deterrent features are inherent in the material, the reformulation would simply focus on adjusting the microstructure of the carrier powders to achieve the drug-release profiles for the chosen compound. Lucideon has the expertise to achieve this through its understanding of the chemistry and physics behind the materials and knowing how to control and modify its technology for the different physicochemical properties of the drugs in question.

#### CONCLUSION

Abuse deterrence is becoming increasingly relevant for not only opioids but also other addictive or high-dose formulations. As the regulatory landscape is becoming clearer and the US government and policymakers continue to place pressure on the industry this will no doubt continue to accelerate the uptake of ADF solutions. Other key factors, including differentiation and market share protection, will also continue to drive development in this area. However the challenges facing the ADF market are many, amongst them are some key issues including product usability for non-abusing patients and, of course, costs of development.

Lucideon’s iCRT-deter aims to strike a balance between tackling abuse, serving non-abusing patients and the manufacturer’s requirements. It offers a controlled release solution with a range of ADF strategies built in, as well as other formulation benefits to reduce manufacturers’ costs and complexity of development, all without compromising usability.

#### ABOUT THE COMPANY

Lucideon focuses on delivering competitive advantage for pharmaceutical manufacturers using novel technologies and development support. Lucideon’s solutions are borne out of materials expertise and ability to cross-fertilise ideas and knowledge across sectors.

Lucideon believes that true innovation is achieved via partnership – scientists working closely with analytical teams, chemical engineers and process engineers in the US and the UK to develop tailor-made solutions for every client.

# When off-the-shelf just won't do

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## TARGETING THE END GOAL: OPPORTUNITIES & INNOVATIONS IN COLONIC DRUG DELIVERY

In this article, Sejal R Ranmal, PhD, Director of Formulation, Vipul Yadav, PhD, Director of Product Development, and Abdul W Basit, PhD, Founder, all of Intract Pharma, describe recent insights into the physiology of the colon, including the increasingly recognised importance of gut flora in human health, disease and pharmaceutical treatment approaches. The authors highlight the advantages of targeting drug release to the colon, and introduce Phloral®, Intract's unique system for achieving drug release in the colon successfully and consistently.

Oral drug delivery to the colon has long been recognised to have several therapeutic advantages. Traditionally, targeting drugs to this region of the gastro-intestinal (GI) tract was viewed as a niche application, innately providing clinical benefits for localised diseases such as inflammatory bowel disease (IBD) or colorectal cancers. However, as rapidly advancing techniques in molecular biology and medical imaging have increased our knowledge of human GI physiology, the colon has emerged as an optimal site for delivery of small molecules and biopharmaceuticals. Evidently, the colon can serve as a favourable site of absorption and provide a valuable pathway for entering the systemic circulation. The emergence of revolutionary new scientific fields including microbiome therapeutics and chronotherapeutics bring promise of a new era of pharmacotherapy via the gut.

To help realise these opportunities, Intract Pharma has developed Phloral®, a dual-action technology enabling fail-safe delivery to the colon in both healthy and diseased states.

### PHYSIOLOGICAL ADVANTAGES OF THE COLON

The human gut is a complex and dynamic environment with many factors influencing

the behaviour of drugs and delivery systems, including the characteristics of luminal contents (e.g. fluid volumes, pH and composition) and the function of intestinal drug metabolising enzymes and transporter systems.<sup>1</sup> These parameters vary in different regions of the GI tract and some can be altered by genetic factors, lifestyle and disease state. An increased understanding of these regional physiological differences continues to uncover important functions relevant to drug delivery. Leveraging the natural physiological advantages of the colon provides opportunities to optimise pharmacological effects.

### The Power of the Gut Microbiome

The human gut harbours trillions of micro-organisms, collectively known as the microbiota. The density of micro-organisms increases substantially towards the distal gut with an exponential rise in the colon. The microbiota can be considered an organ in itself, with an intrinsic metabolic capacity that is implicated in the biotransformation of drugs and other xenobiotics.<sup>2,3,4</sup> Degradation mediated by gut bacteria has been observed for as many as 40% of tested drugs. Despite the diversity in their chemical structures, two broad transformation patterns are most frequently observed – reduction and



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hydrolysis. This phenomenon can be used to an advantage in drug development through strategically designed prodrugs such as sulfasalazine, for ulcerative colitis, and the antibacterial prontosil. In other cases, it is valuable to determine the consequences of microbial metabolism of drugs and their metabolites, including effects on efficacy and toxicity.

Pioneering science is beginning to uncover the complexities of the symbiotic relationship between microbe and man, and determine its role in human health and disease.<sup>5</sup> This is leading to the development of a new generation of therapeutics based on, or targeted at, the gut microbiome. This complex and dynamic ecology of over 1000 bacterial species is integral to host digestion and metabolism, defence against pathogens and interactions with both the immune and nervous systems. As such, the gut microbiome has been implicated to play a role in numerous pathologies including inflammatory diseases, diabetes, obesity, neurological disorders (including Alzheimer's disease and Parkinson's disease) and immuno-oncology.<sup>5</sup> To confer their modulatory effects, many live biotherapeutic products (LBPs) and microbiome therapeutics necessitate targeted delivery to the colon where the largest contingent of gut microbiota reside. Numerous studies have also demonstrated that probiotic species are intolerant to gastric juices and the harsh environment of the stomach and small intestine.<sup>6,7</sup> In contrast, an orally administered Phloral<sup>®</sup> coated microbial therapeutic has demonstrated improved efficacy and successful, stable engraftment of a full diversity of healthy microbiota in patients treated for recurrent *Clostridium difficile* infection.<sup>8</sup>

#### Reduced Drug Efflux Transporters and Metabolising Enzymes

The presence and function of intestinal drug transporters and mammalian drug metabolising enzymes has a profound effect on oral drug absorption, and the significance of intestinal first-pass metabolism should not be underestimated.

Recent studies employing gene expression and protein abundance techniques have established that the longitudinal expression of numerous intestinal transporters varies across the length of the human gut.<sup>9</sup> In particular, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are two clinically relevant efflux transporters implicated in limiting the bioavailability of

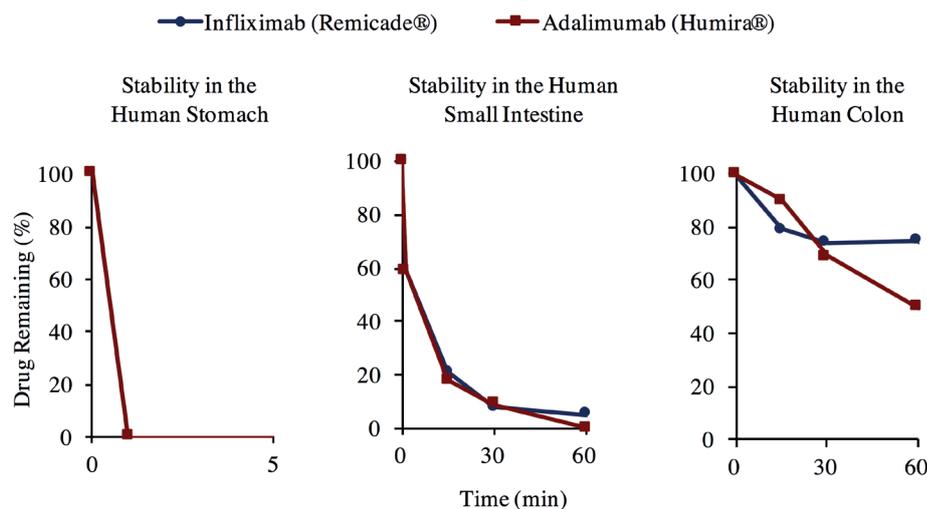


Figure 1: Stability of therapeutic monoclonal antibodies in human gastric fluids, human small intestinal fluids and human colonic fluids. Biopharmaceuticals show improved luminal stability in the colon compared with the proximal regions of the gut. Adapted from Yadav *et al* (2016).<sup>16</sup>

“Phloral<sup>®</sup> is the world's first and only dual-trigger coating technology which has demonstrated precise, fail-safe release in the colon in both healthy and diseased states.”

many structurally diverse drug substrates by pumping them back into the gut lumen. The mRNA expression and protein content of both P-gp and BCRP are significantly lower in the colon compared with the small intestine.<sup>10</sup>

With a few exceptions, most drug metabolising cytochrome P450 enzymes also demonstrate lower levels of expression in the colon, which can have important implications for drug effects.<sup>11</sup> For example, simvastatin, a CYP3A4 substrate, showed three times greater oral bioavailability when delivered to the distal gut (delayed-release formulation) compared with the proximal gut (immediate-release formulation).<sup>12</sup> Identifying and targeting the optimal site of drug absorption provides opportunities to naturally enhance oral bioavailability.

Oral delivery of biopharmaceuticals remains a “Holy Grail” in drug development, however a formidable array of physical and chemical barriers in the gut have permitted only a very small number of oral products to reach the market thus far. Poor drug stability and permeability in different regions of the gut have been major obstacles in achieving bioavailability. The proximal small intestine appears to be favourable for uptake. However, this region also presents the greatest enzymatic barrier, with lumenally secreted proteases and membrane-bound peptidases leading to significant degradation.<sup>13</sup>

In contrast, the colon benefits from comparatively less proteolytic activity compared with both the stomach and small intestine. Cutting-edge research utilising biorelevant human GI fluids has demonstrated that biologics, including proteins, peptides and monoclonal antibodies show significantly improved luminal stability in the colon compared with the proximal regions of the gut, as illustrated in Figure 1.<sup>14, 15, 16</sup> Targeting drug delivery to the colon presents important advantages which can be used alongside complementary strategies to improve stability and permeability further (e.g. using protease inhibitors or permeability enhancers). This combined approach is likely to be the most successful in helping to realise the promise of orally administered biopharmaceuticals.

#### Luminal Conditions and Transit

Historically, lack of fluid volumes in the colon has been perceived as a primary limitation for targeted drug delivery. Although free fluid volumes have shown to be variable and sometimes limited,<sup>17</sup> magnetic resonance imaging studies have shown typical filling volumes in the colon to be high, averaging over 200 mL in healthy fasted subjects.<sup>18</sup> These modern techniques have also demonstrated that fluid volumes in the small intestine are

not homogeneously distributed but segregated in “fluid pockets” of varying volume.<sup>19</sup> Mean small intestinal fluid levels of 50-100 mL have been reported after overnight fasting.<sup>19</sup> As such, it is useful to evaluate drug solubility under biorelevant colonic conditions to determine the inherent behaviour of molecules in this unique environment.

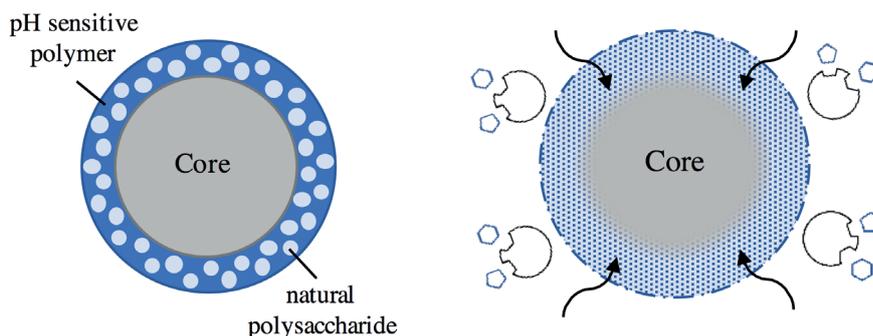
Transit times through the colon are significantly longer compared with the small bowel (on average over 24 hours *versus* four hours respectively in healthy adults), which encourages contact with absorptive surfaces and subsequently can improve drug uptake.<sup>11</sup>

Transit times through the gut can also be exploited to implement a revolutionary therapeutic approach known as chronotherapy. Increasing evidence demonstrates that certain physiological functions, disease pathologies and the pharmacological effects of drugs can exhibit circadian rhythms.<sup>20</sup> Co-ordinating the timing of drug treatments with these biological effects can be used to maximise efficacy and minimise adverse effects. An orally administered formulation targeted to the colon needs to traverse the entire alimentary canal in order to reach the target site. Using this intentional time delay in absorption can facilitate effective symptom control and disease management. For example, symptoms of certain diseases such as rheumatoid arthritis, asthma and hypertension are known to manifest in the morning upon rising. Administering medicinal products at night and synchronising colon targeted release in the early hours enables patients to wake up symptom free.

### DETERMINING DRUG BEHAVIOUR IN THE GI TRACT

An increasing number of drugs in the development pipeline exhibit poor solubility, poor permeability or both. It has therefore never been more important to determine drug behaviour in specific regions of the GI tract accurately and establish optimal drug delivery strategies at an early stage. Intract has developed specialist gastrointestinal stability and permeability models as rapid and cost-effective means to evaluate drugs using biorelevant fluids and tissues from preclinical species and humans. The models have been used to evaluate the stability of numerous small molecules and biopharmaceuticals to provide unparalleled

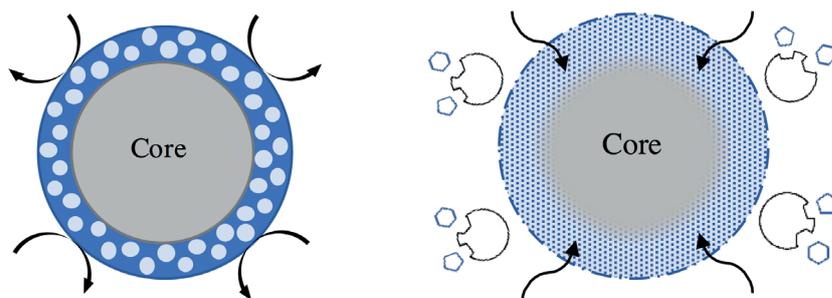
#### A: Typical Dual-trigger Mechanism



Phloral® incorporates a pH sensitive polymer and natural polysaccharide as a combination single film coating

The pH sensitive polymer dissolves at a higher pH towards the colon and the polysaccharide is digested by trillions of bacteria naturally residing there

#### B: Fail-safe Mechanism in Subjects with a Variable Gastrointestinal pH



Even if the correct luminal pH is not reached to trigger dissolution of the pH sensitive polymer

The polysaccharide is digested by the microbiota as an independent fail-safe mechanism to guarantee release in the colon

Figure 2: Phloral’s unique dual-action mechanism exploits changes in gastrointestinal pH in combination with the enzymatic activity of the colonic microbiota as independent but complementary triggers to guarantee site-specific release.

insights into human GI behaviour, as highlighted in Figure 1.<sup>14,15,16,21,22</sup>

Intract’s colon simulation model uses biorelevant inoculum, proprietary media, and a specialist anaerobic work-station to mimic the conditions of the large intestine accurately. Intract’s *ex vivo* Ussing chamber system can also be used to study the absorption and translocation of compounds across the intestinal wall from specific regions of the GI tract, including the colon. Strategic clinical collaborations provide unique access to biological fluids and tissue samples from healthy human subjects, as well as patients with GI diseases. Intract’s comprehensive knowledge and capabilities can support preclinical development and provide unique insights to improve delivery strategies for greater clinical success.

### PHLORAL® FOR PRECISE FAIL-SAFE DELIVERY TO THE COLON

Despite the well-established advantages of colonic drug delivery, achieving consistent, site specific release in this region of the gut has historically proven to be a challenge. The most common approach has relied on pH sensitive polymers which are designed to dissolve at the higher pH towards the terminal ileum. However, these conventional approaches have demonstrated significant variability and failure *in vivo*, with drug release occurring prematurely or, in some cases, not at all.<sup>23-26</sup> This is unsurprising given the vast inter- and intra-subject variability in critical parameters affecting formulation behaviour, including pH, fluids volumes, transit times and motility.

Phloral® is the world's first and only dual-trigger coating technology which has demonstrated precise, fail-safe release in the colon in both healthy and diseased states. This innovative system comprises of a pH sensitive polymer in combination with a natural polysaccharide that is specifically digested by the colonic microbiota (Figure 2).

The pH and enzymatic triggers work in a complementary manner to facilitate site-specific release. However in instances where the dissolution threshold of the pH responsive polymer is not reached, the polysaccharide component is independently digested by enzymes secreted by the trillions of diverse bacterial species naturally residing in the colon. This additional fail-

safe mechanism overcomes the limitations of conventional polymer coatings, as demonstrated in an *in vivo* study with human subjects.

Phloral® was evaluated against Eudragit® S, a widely used commercial pH sensitive coating. Radiolabelled tablets were coated and administered under various feeding regimens to eight healthy adults, with transit and disintegration tracked by gamma scintigraphy. All Phloral-coated tablets released in the colon whereas in the fed state, almost 40% of Eudragit® S coated tablets failed to release and were voided intact in the stool. Phloral® demonstrated 100% successful release under fed, fasted and pre-feed states (Figure 3).<sup>27</sup>

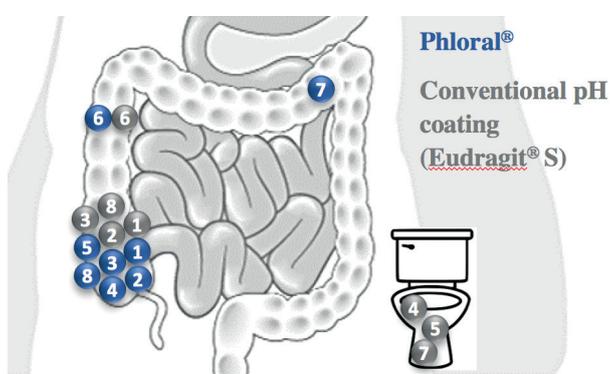


Figure 3: Phloral was evaluated against Eudragit S, a conventional pH sensitive coating, in an *in vivo* gamma scintigraphy study. Tablets illustrate the site of disintegration in 8 individual subjects in the fed state. Conventional tablets remained intact in subjects 4, 5 and 7 and passed out in the stools.

Phloral® is a patent protected technology and is available for licence exclusively from Intract Pharma. The first commercial product harnessing the power of the Phloral® technology has successfully completed phase III clinical studies, with the new once-daily formulation showing significantly improved maintenance of remission in patients with ulcerative colitis.<sup>28</sup> Other licensed products are in different stages of

“The first commercial product harnessing the power of the Phloral® technology has successfully completed phase III clinical studies, with the new once-daily formulation showing significantly improved maintenance of remission in patients with ulcerative colitis.”

clinical development across a wide range of therapeutic indications. The technology utilises generally regarded as safe (GRAS) materials and requires conventional manufacturing equipment.

Targeted drug delivery using Phloral® provides unprecedented opportunities to exploit the natural physiological advantages of the colon to develop advanced new therapeutics with the potential to revolutionise patient care.

## ABOUT THE COMPANY

Intract Pharma Ltd is a licensing and product development company offering state-of-the-art drug delivery technologies and advanced GI models for product innovation. A spin-out of University College London, Intract is centred around more than 20 years of research and innovation from the laboratory of Professor Abdul Basit.

Intract specialises in oral drug delivery and offers a range of proprietary technologies to help overcome formulation challenges and enhance product performance. Complementary to these, Intract has developed unique GI models as strategic tools to provide expert analysis of drug and formulation behaviour under physiologically appropriate conditions. Intract's drug delivery technologies have been licensed across various therapeutic indications and in-house research and development pipeline includes the preclinical evaluation of a range of products with strong scientific and commercial promise. Using specialist knowledge and experience, Intract can help establish the pathway from successful early stage preclinical development through to clinical and commercial manufacture.

## ABOUT THE AUTHORS

**Sejal Ranmal**, PhD, is Director of Formulation at Intract Pharma and has a research background in paediatric formulation development. Before joining Intract, Dr Ranmal completed her Pharmacy degree and PhD in Pharmaceutics from University College London (UCL) School of Pharmacy, London, UK.

**Vipul Yadav**, PhD, is Director of Product Development and has expertise in overcoming biological barriers to achieve oral administration of biopharmaceuticals. Dr Yadav received an MSc in Drug Delivery where he researched oral peptide delivery. He then completed a PhD in Pharmaceutics at UCL School of Pharmacy exploring the biological mechanisms involved in oral delivery and intestinal uptake of anti-TNF- $\alpha$  monoclonal antibodies.

**Abdul Basit**, PhD, is Professor of Pharmaceutics at UCL School of Pharmacy. Professor Basit's research sits at the interface between pharmaceutical science and gastro-enterology, forging links between basic science and clinical outcomes. He is an international authority on oral drug delivery and absorption, and has published over 300 papers, book chapters, abstracts, and patents. He leads a large and multi-disciplinary research group, and the goal of his work is to further the understanding of GI physiology by fundamental research. He is a frequent speaker at international conferences, serves as a consultant to numerous pharmaceutical companies and is on the advisory boards of healthcare organisations, charitable bodies and scientific journals.

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## SINGLE-STEP FUNCTIONAL COATINGS FOR INCREASED EFFICIENCIES

In this article about oral drug innovation, Cory Berkland, PhD, Co-Founder & Chief Scientific Officer, and Nathan Dormer, PhD, Vice-President of Research & Development, both of Orbis Biosciences, focus on how enterics and reverse enterics are applied into dosage forms, and discuss the future of this class of drug formulation technology.

Drug formulation and delivery focuses on preserving active pharmaceutical ingredient (API) function while the drug is ushered to the specific site of absorption and/or action at the right time and in the right quantities. This can be a difficult task considering the physical, chemical and biological obstacles the human body presents. The natural impediments the body presents are the primary reason so many drug delivery approaches exist.

"In the simplest circumstances, enterics are used either to prevent gastric mucosal irritation or to protect pH-labile APIs from degradation.

Reverse enterics are primarily used to bypass the oral mucosa (for taste and odour masking), while maintaining immediate-release behaviour once reaching the stomach."

One of the oldest and simplest routes of administration, oral delivery, is no stranger to formulation evolution. Oral dosage forms have arguably seen the most progressive transformation, advances building on each other over time leading to innovation and invigoration of traditional pills, tablets and capsules. One of the most useful inclusions for creating next-generation oral dosage forms are pH-responsive materials, colloquially referred to as enterics and reverse enterics.

Enterics and reverse enterics, typically applied as pill or tablet coatings, are only soluble in specific pH ranges, which enables them to have site-specific gastro-intestinal release, such as the mouth, oesophagus, stomach, and specific regions of the small and large intestines. In the simplest circumstances, enterics are used either to prevent gastric mucosal irritation or to protect pH-labile APIs from degradation. Reverse enterics are primarily used to bypass the oral mucosa (for taste and odour masking), while maintaining immediate-release behaviour once reaching the stomach.

The most widely used methods for applying enteric and reverse enteric coatings involve solvating or dispersing the coating powder in an aqueous or organic species then spraying the coating solution onto the



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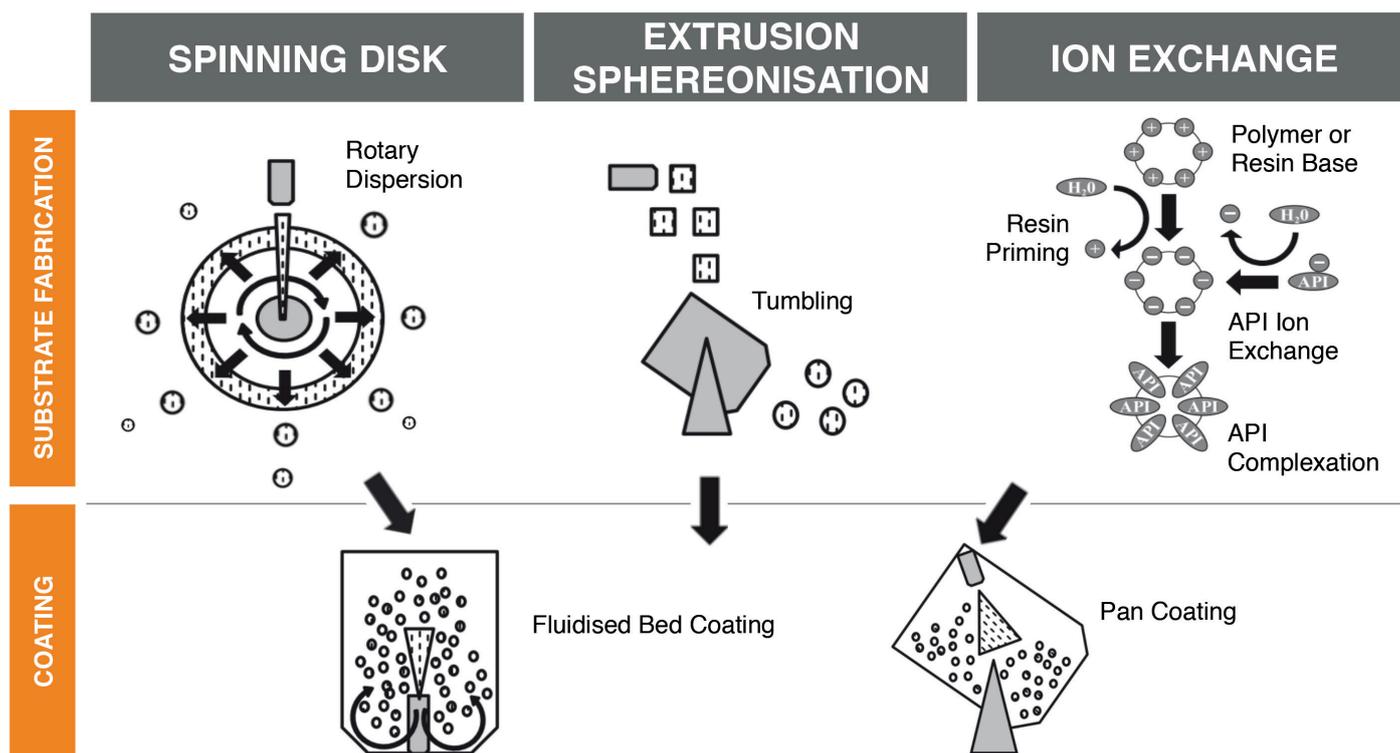


Figure 1: Coating of tablets, capsules and dispersed dosage forms begin with creation of the substrate core. Then, in a second step, enterics or reverse enterics are applied as coatings.

pill or tablet using pan coating or fluid bed coating. Notably pan coating and fluid bed coating are batch processes with multiple steps (Figure 1).

Pan coating (which in reality utilises a rotating drum) allows the tablets or substrate to tumble while an enteric or reverse enteric solution is sprayed on at a controlled rate. Newer pan coating machines have an internal drum layer that is perforated, which allows for more expedient evaporation of the coating solvent and subsequent hardening of the coating layer.

Fluid bed coating utilises a similar spray-on approach, but greatly increases the inter-tablet or inter-substrate space by using air to circulate the mini-tablets, pills, etc, and then dry them, all in the same piece of equipment. This allows very small substrates to be coated, but at the cost of using large volumes of solvent solution and subjecting the substrate to high shear stresses during circulation, which can negatively affect coating friability. Fluid bed coating, however, is relatively quick compared with pan coating.

Nonetheless, despite the theoretical simplicity of pan coating and fluidised bed coating, the processes involve extensive validation of coating thicknesses within a batch, between batches, and the general tolerances of those thicknesses in terms of product quality and reproducibility. Just

“The ability to coat drug-loaded cores completely with enterics and reverse enterics allows Orbis’ manufacturing platform to combine modified-release dosage forms with the desirable form factor of microparticulates.”

one region on a tablet or pill with a thinner applied coating can compromise the intended performance of the entire dosage form. A technique to circumvent the difficulties of achieving a consistent coating is to utilise microparticles rather than one large pill. The microparticles are sieved prior to performing pan or fluid bed coating with the intent of increasing the probability of batch contents receiving an even coating. The particles are then coated with the enteric or reverse enteric and utilised as a drug product intermediate for capsules, sachets or even liquids. Although this process has a burdensome number of steps, microparticles provide superior format flexibility, taste-masking, dosing routes and the potential to circumvent food effects.

Whether utilised for a tablet or microparticle application, enterics and reverse enterics are seldom used in a standalone manner, and are commonly applied over other materials that exhibit modified-release properties (such as

extended-release polymers) or excipients that enhance solubility and/or permeability. In other instances enteric and reverse enteric coatings are used in conjunction with one another to achieve specialised release profiles for one or multiple APIs. Considering scenarios like this, one can see that traditional approaches for creating modified-release solid oral dosage forms can easily involve several batch-wise steps, compounding time, personnel and operating expenses.

In addition to the incremental cost associated with multiple coating and validation steps these processes often result in variable coating thicknesses that can affect product performance.

The most obvious fix to the burden of multiple coating steps is to create a technique that consolidates all of the necessary excipients and coatings into one manufacturing step. Specifically it is to apply the coating at the same time the tablet or pill is fabricated. Historically the physical

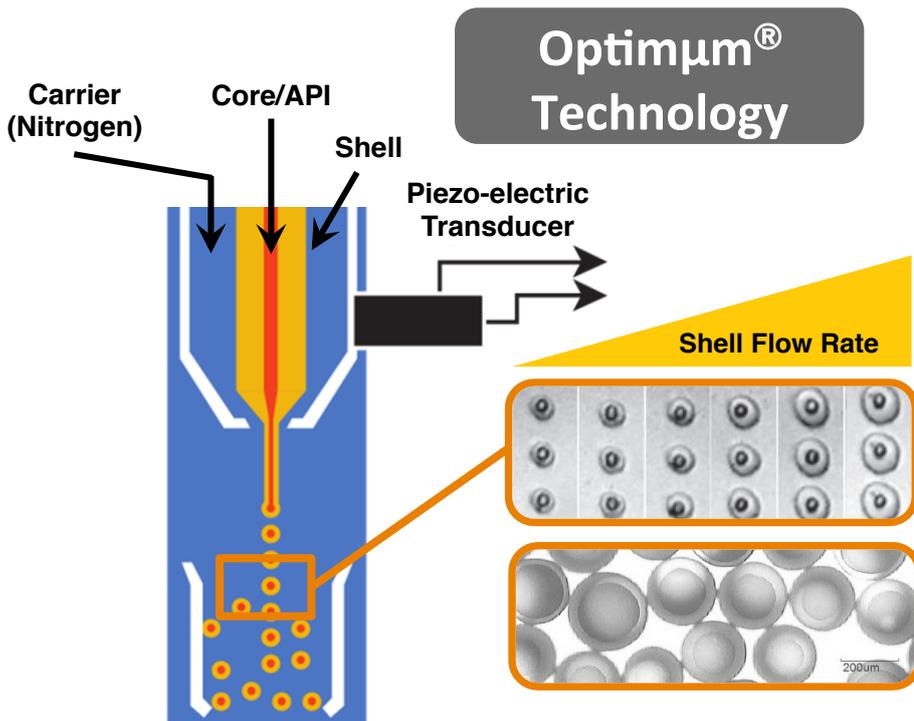


Figure 2: Orbis' Optimum® technology can apply an enteric or reverse enteric coating over an API-rich core in a single manufacturing step, which eliminates the need for pan or fluid bed coating and provides the additional advantage of having a particulate dosage form that can be used as a stand-alone solution or integrated into other oral dosage forms, such as capsules or orally-disintegrating tablets.

ability to do this has not been available due to the coating solutions being liquid when applied and the tablet compression mechanism not allowing for application of said liquid. However, at Orbis we have developed a process to coat the substrate (with an enteric, reverse enteric or any polymeric material) simultaneously as the substrate itself is being created. Orbis' proprietary Optimum® technology uses two

liquid streams flowing through concentric nozzles to achieve a coated microsphere in a single manufacturing step.

Optimum® technology allows processing of viscous wax, lipid, enteric and API solutions through a vibrating nozzle to make small coated microspheres ("microcapsules") which behave like tablets, all in a single step (Figure 2). Using simple process parameters, such as flowrate

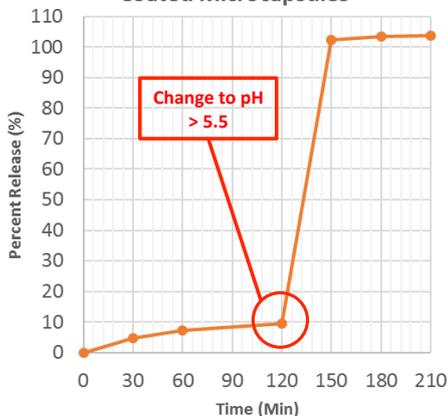
"Beyond the lens of industrial efficiency, the ability to provide controlled-release kinetics with format-flexible dosage forms is fundamental for serving specific, large populations. When considering just paediatrics and geriatrics, dosage forms that cannot be swallowed or cause difficulty swallowing affect over half of the global population. However the need extends well beyond these patient populations as there are specific therapies and indications that induce dysphagia, even in healthy adults."

and frequency of vibration, Optimum® technology can create microcapsules with various shell thicknesses and overall sizes, which enable tailoring of release profiles and high API content for such a small form factor. The ability to coat drug-loaded cores completely with enterics (Figure 3a) and reverse enterics (Figure 3b) allows Orbis' manufacturing platform to combine modified-release dosage forms with the desirable form factor of microparticulates. In addition to single-step coating, Optimum® technology retains superior control over microsphere size distribution, enabling highly accurate and reproducible manufacturing scale, powder dosing, API release and therapeutic performance.

With the wide array of enteric and reverse enteric polymers available it stands to reason that new technologies such as the Optimum® platform will utilise these complex chemistries in unique ways, putting new spins on old dosage forms. This seemingly simple switch from a multi-step process to a single step process provides the industry with the opportunity to increase manufacturing efficiency and lower costs whilst eliminating coating variability for improved product performance.

Beyond the lens of industry efficiency, the ability to provide controlled-release kinetics with format-flexible dosage

a) Release of Ibuprofen From Enteric-Coated Microcapsules



b) Release of Ritonavir From Reverse Enteric-Coated Microcapsules

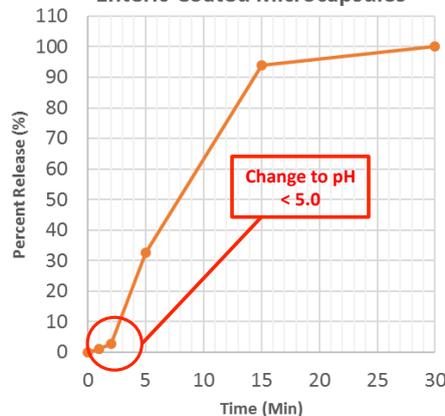


Figure 3: Orbis' Optimum® technology during dissolution testing showing (a) release of ibuprofen from an enteric-coated microcapsule of diameter 250 µm occurs when the powder is exposed to neutral conditions after an acid soak test of two hours and (b) release of ritonavir from reverse enteric-coated microcapsules of diameter 250 µm occurs when the powder is exposed to low pH conditions similar to the gastric mucosa.

forms is fundamental for serving specific, large populations. When considering just paediatrics and geriatrics (under 18 and over 65 years of age), dosage forms that cannot be swallowed or cause difficulty swallowing affect over half of the global population. However the need extends well beyond these patient populations as there

are specific therapies and indications that induce dysphagia, even in healthy adults.

The evolution of oral dosage forms to include enterics and reverse enterics showcases the industry's ability to develop solutions for protecting both patient and API. The current multi-step processes needed to manufacture enteric and reverse

enteric dosage forms achieve the desired effect but are burdensome and wasteful, often missing the mark in terms of patient palatability or product performance. Orbis' Optimum® technology provides an elegant solution by condensing all manufacturing steps into one. This solution comes with the added benefit of creating a dispersed, microcapsule dosage form that is ideal for use in multiple format types serving a broad range of patient populations.

## ABOUT THE AUTHORS

**Nathan Dormer, PhD**, is Vice-President of Research & Development at Orbis Biosciences. He has a decade of experience developing a variety of controlled-release solutions using microsphere techniques. He received his BS in Chemical Engineering from The University of Kansas (Lawrence, KS, US) before completing his PhD in Bioengineering with Honors from The University of Kansas with NIH-sponsored training in drug delivery and protein stability. He has authored a number of publications and book chapters relating to microsphere encapsulation and has direct experience formulating dozens of active pharmaceutical ingredients.

**Cory Berkland, PhD**, is the co-founder and Chief Scientific Officer of Orbis Biosciences. He has been developing micro-encapsulation and drug delivery capabilities for more than a decade. He has a PhD in Chemical and Biomolecular Engineering from the University of Illinois, Urbana-Champaign, where he co-invented and developed the Orbis technology. Dr Berkland is also a Professor of Pharmaceutical Chemistry and Chemical and Petroleum Engineering at the University of Kansas.

## ABOUT THE COMPANY

Orbis Biosciences partners with pharmaceutical companies to optimise their oral and injectable product portfolios. Orbis delivers uniformly sized microspheres and microcapsules for precise control over release kinetics in a single manufacturing step. Oral products enabled by Orbis' Optimum® technology feature taste-masking, extended-release and delayed-release options in patient friendly formats. Injectable products enabled with Orbis' Stratum™ technology include extended-release and a market pioneering pulse-release option.



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# CAN WE ACHIEVE EFFECTIVE ORAL DELIVERY OF VACCINES? EVALUATING A NEW MICROSPHERE BASED CONTROLLED-RELEASE DELIVERY SYSTEM

By S Mohan Mohanraj, PhD, and Meir Kende, PhD

## ABSTRACT

In recent years, therapeutic proteins, such as vaccines, antigens, and hormones, have made significant advances using sophisticated biotechnological techniques like recombinant technology. However, the mode of administration has been a limiting factor. Frequent injections and low patient acceptability make even the simplest parenteral administration of these drugs problematic, thus there is a need for new delivery systems to deliver these drugs more effectively. Oral delivery of proteins and peptides has long been hailed the holy grail of drug delivery for obvious reasons (i.e. ease and cost of administration, patient compliance and acceptability) but has remained a challenge due to enzymatic degradation in the gastro-intestinal (GI) tract and low bioavailability.

Here we evaluate a microsphere based controlled-release delivery system that appears to have promising results. PolyMicrospheres successfully developed an oral delivery system for a recombinant vaccine that resulted in an antibody titre count three times higher than parenteral delivery. The microsphere based delivery system greatly enhanced immunity: 100% survival of mice against the toxin and 88% survival of rabbits against the live bacterial spores, compared with 0% survival with the aqueous recombinant protective antigen (RPA) system.

## OBJECTIVES

The objective of this work was to develop novel antigen-adjuvant delivery systems to enhance the efficacy of RPA via oral immunisation against anthrax. To demonstrate

that effective protection against anthrax spores can be achieved by alternative oral, needle-free vaccination, PolyMicrospheres developed and evaluated the efficacy of microsphere based delivery systems. The efficacy of vaccination can be considerably improved, not only by incorporating the antigen in a matrix, but also by incorporating potent adjuvants in the matrix to provide long-term delivery of antigen together with an adjuvant for further potentiation of the immune response. The goal was to design and develop an oral RPA delivery system with controlled-release kinetics over a period of months, stimulating an enhanced antibody response at many distinct time points for long lasting protection.

## BACKGROUND & SIGNIFICANCE

In response to anthrax being the most prominent threat in biological warfare, a recombinant PA vaccine was developed offering significant protection.<sup>1,2,3</sup> Vaccination with the first generation of anthrax vaccine, after the initial injection

“Administering the vaccine in a micro-encapsulated delivery system protects against the acidic environment in the stomach, thereby its native form is preserved, which is critical for antibody maturation and immunogenicity.”



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in the presence of alum adjuvant, requires five booster doses in 18 months. Additionally side-effects can occur, ranging from local soreness to fever and illness, with increased chance of occurrence after a booster injection. Recombinant protective antigen with alum adjuvant (a second-generation vaccine) still requires three to four vaccinations over an 18 month period, thus there is an obvious need for a safe and effective self-administered oral vaccine delivery system which can elicit full protection after a few weeks of vaccination. In this applied research we developed and evaluated novel microsphere based antigen-adjuvant oral delivery systems to enhance the efficacy of RPA vaccine. This platform technology could be utilised not only against inhalation anthrax but also against other microbes and toxins.

### OVERCOMING THE CHALLENGES OF ORAL DELIVERY

Mucosal surfaces of the GI tract and the nasal passages are the major portals of entry of infectious agents and microbial toxins, therefore the mucosal surfaces constitute the first line of defence. Oral vaccination strategies that enhance mucosal immunity have practical significance to protect military personnel and civilian populations against biological weapons and other microbes. Vaccination by the oral mucosal route stimulates sIgA in the GI tract and lungs, while also stimulating systemic immunity,<sup>4</sup> thus mucosal vaccination elicits a broader immune response, as well as enhanced systemic and topical protection. The efficacy of the vaccine is substantially enhanced by a mucosal adjuvant; consequently a powerful systemic and mucosal immunoglobulin (IgG and IgA) response is stimulated, thereby providing a very potent first-line protection against oral and intranasal entry of microbes and toxins.

Oral administration of a vaccine possesses all the prerequisites for a simple, safe and effective route of vaccination. Although the mucosal surfaces of the GI tract represent a large area, only the ileum with its neutral pH has the proper environment for effective presentation of orally administered vaccine. Numerous studies have demonstrated that for oral stimulation of high immunoglobulin levels frequent administration of high doses of the aqueous vaccine is required.<sup>5</sup> However while oral vaccination with multiple doses of aqueous vaccine can be rendered more effective in the presence of a mucosal adjuvant, even then several doses

“These microsphere based delivery systems can be designed in such a way that they not only protect their content from the digestive enzymes but also deliver it at desired intervals.”

will likely be required for vaccination. Also one drawback of oral administration of protein antigens is that they are broken down in the upper GI region by digestive enzymes and hence lose their immunogenicity.

Administering the vaccine in a micro-encapsulated delivery system protects against the acidic environment in the stomach, thereby its native form is preserved, which is critical for antibody maturation and immunogenicity.<sup>6</sup> The uptake of microspheres is enhanced by the endocytic M-cells lining the intestine. Microspheres can be taken up from the intestine into the immune-inductive environment of the Peyer's patches, where they can induce both mucosal and systemic immune responses. These microsphere based delivery systems can be designed in such a way that they not only protect their content from the digestive enzymes but also deliver it at desired intervals. Controlled release of antigens from polymer microparticles has been of particular interest in the development of vaccine delivery systems.<sup>6,7</sup>

The efficacy of vaccination can be improved not only by incorporating the antigen in the polymer matrix, but also by incorporating potent adjuvants in the matrix to provide long-term delivery of antigen together with a vaccine-adjuvant for further potentiation of the immune response. Many modern vaccines are composed of highly purified or recombinant proteins or synthetic peptides. The use of potent adjuvants (such as CpG

motifs, lipopolysaccharide, polyIC, monophosphoryl lipid A,<sup>8,9</sup> LTR72 and LTK63<sup>10</sup>) to enhance immune response to these antigens is an attractive method for improving their immunogenicity.

Vaccine delivery by the oral route is not easy to achieve, but if it is possible the preparation can be packaged in a stable form that is easy to administer.

### METHODOLOGY

The microsphere based delivery systems (MDSs) were tailor-made to suit the oral administration route. In many stages PolyMicrospheres has designed, developed, and evaluated third-generation anthrax vaccine delivery systems specifically for oral administration. Each stage consists of a group of optimal formulations with various diameters, polymer matrices and/or with different loadings to provide controlled (or pulsatile) release of the recombinant anthrax vaccine.

In order to achieve full protection by oral immunisation the delivery system needed to be designed to perfection and developed with optimal micro-encapsulation methods and release kinetics. The MDSs comprised a combination of the following: the second-generation RPA, a potent mucosal adjuvant (ADJ), optimal RPA-adjuvant ratio, proper drug loading, poly(lactide/glycolide) ratio for the ideal half life, microsphere particle diameter to penetrate into and be retained by the mucosal epithelial cells of the intestinal tract, and the process parameters to achieve the stability and integrity of the conformation of RPA.

We focused significantly on the design and development of the RPA- and ADJ-incorporated MDSs. A mucosal adjuvant such as LTK-63 was incorporated with the recombinant protective antigen into biodegradable polymer microspheres to provide a long-term delivery of a vaccine adjuvant for further potentiation of the immune system. Selected RPA- and ADJ-encapsulated microsphere matrices were further coated with a bio-adhesive

“Our orally delivered MDS-Q showed extremely high IgG titres throughout the 108-day testing period, exhibiting a two- to three-fold increase over the parenterally delivered positive control (and a 50-fold increase over the aqueous RPA system).”

“Oral vaccination with an MDS offers several key advantages over parenteral administration: it reduces immunisation time, can be self-administered, and can be packaged in a stable form as a pill. On a macro level it simplifies the logistics of immunisation to large populations by increasing compliance and eliminating the need for medical personnel, thus increasing availability and lowering the system cost.”

(MDS-BioAd) to promote the adhesion, retention and uptake of the microparticles into the mucosal membranes of the intestine.

The RPA/adjuvant delivery systems were designed to provide controlled- and/or pulsatile-release delivery of the recombinant anthrax vaccine and the adjuvant. Depending on the optimal combination of the RPA/ADJ in the polymer matrix, the molar ratio of lactide-glycolide, drug loading, particle diameter and the micro-encapsulation methods and process techniques, the contents are released in a controlled manner at multiple time points stimulating antibody peaks several weeks apart, thereby providing long-lasting immunity and protection. The delivery systems were designed such that the antigen can reach the mucosal antigen processing cells in its native conformation for induction of an effective protective immunity. The MDS formulations were prepared with the following parameters:

- Matrix materials: poly(dl-lactide-co-glycolide) and poly(dl-lactide)
- Microsphere mean diameter range: 6-20 µm
- RPA of anthrax (from List Biological Laboratories, Campbell, CA, US)  
Loading: 0.5-1%
- Adjuvant (LTK63 from (Chiron, Italy)  
Loading: 0.04-0.13%
- MDS products were prepared using established protocols currently in use at PolyMicrospheres.<sup>11</sup> A modified complex coacervation process was used. Selective MDS microspheres were further coated with a solution of a bio-adhesive polymer.

#### Analytical Methods for the Characterisation & Stability Studies

The MDS products developed were characterised as to mean particle diameter, size distribution, antigen and adjuvant loadings using established protocols currently in use at PolyMicrospheres.

#### Protocols for Vaccination Of Mice & Efficacy Studies

A/J mice were immunised with 7-8 mg of each MDS by a two-dose oral administration. The second dose was administered 20 days after the first immunisation with the same dosage of each MDS. Control groups include aqueous RPA system and non-immunised control. Mice were bled from the retro-orbital sinus over a period of 31-108 days after immunisation.

#### ELISA Assay for Mouse Anti-PA Antibodies

Individual serum samples bled at various time points after immunisation were assayed for anti-PA immunoglobulins using standard ELISA protocols. Horseradish peroxidase-labelled anti-mouse antibody directed against IgG was used. The amount produced was determined spectrophotometrically. A standard curve was prepared using known amounts of purified mouse anti-PA antibodies, obtained from USAMRIID as a positive control, and the amount of anti-PA antibodies in the samples was determined.

#### Anthrax Toxin Challenge Studies in Mice

Selective MDS formulations were tested for their efficacy in inducing protection against a lethal challenge of anthrax toxin. Control groups include an aqueous RPA system and a non-immunised group. The anthrax toxin challenge was performed 110 days after immunisation. This challenge consisted of intravenous injection of a mixture of lethal factor (1.5 mg/kg) and protective antigen (3 mg/kg) in a combination equivalent of approximately five LD<sub>50</sub> in non-immunised mice. On day 42 after the toxin challenge the experiments were terminated.

#### Protocols for Immunisation of Rabbits & Efficacy Studies

New Zealand White rabbits were immunised with 30-32 mg of each MDS by a two-

dose oral administration. The second dose was administered 21 days after the first immunisation with the same dosage of each MDS. Control groups include aqueous RPA system and non-immunised control. The rabbits were bled from the ear vein 18, 25, and 32 days after immunisation.

#### ELISA Assay for Rabbit Anti-PA Antibodies

The ELISA assay for the rabbit experiments was similar to that described above for measuring mouse anti-PA antibodies except that horseradish peroxidase-labelled anti-rabbit Ig antibodies were used.

#### Anthrax Spore Challenge Studies in Rabbits

The immunised rabbits were challenged after 42 days with a lethal aerosol exposure of live *Bacillus anthracis* (Ames) spores and monitored for survival. All animals were aerosol-challenged with a target dose of 200 LD<sub>50</sub>. Animals were observed twice daily for 14 days post-challenge for clinical signs of disease including lethargy and respiratory distress. All B anthracis challenges were performed in a BL-3 containment laboratory.

#### Protocols for the Safety & Histopathology Studies

Four to six weeks after immunisation with selected MDS formulations, mice/rabbits at each time point were sacrificed for complete organ histopathology to rule out toxic side effects. At these time points blood samples were collected prior to sacrificing the mice/rabbits for routine serum chemistry including liver and kidney function tests, creatinine kinase, and complete haematology parameter determinations.

## RESULTS & DISCUSSION

With the expertise PolyMicrospheres has in this area we were able to develop, test, and refine the formulations as we progressed through each stage of the animal studies. As the formulations were developed, they were tested systematically in mice. Based on ELISA immunoglobulin titres in mice, prototype formulations were then developed for efficacy studies in rabbits. We developed more than forty MDS products to achieve desired release kinetics by using established micro-encapsulation process protocols currently in practice at PolyMicrospheres. Only very selective MDS products with significant results are reported in Table 1 and discussed here.

Product code	Mean Diameter (µm)	Drug Loading (%)		Type
		RPA	ADJ	
MDS for mouse studies:				
MDS-P	12	0.88	0.08	MDS
MDS-Q	13	0.87	0.08	MDS-BioAd
MDS-R	9	0.82	0.04	MDS
MDS-S	18	0.81	0.04	MDS-BioAd
MDS for rabbit studies:				
MDS-T	7	0.49	0.13	MDS
MDS-U	7	0.48	0.13	MDS-BioAd

Table 1: MDS incorporated with both RPA and ADJ for two-dose oral immunisation.

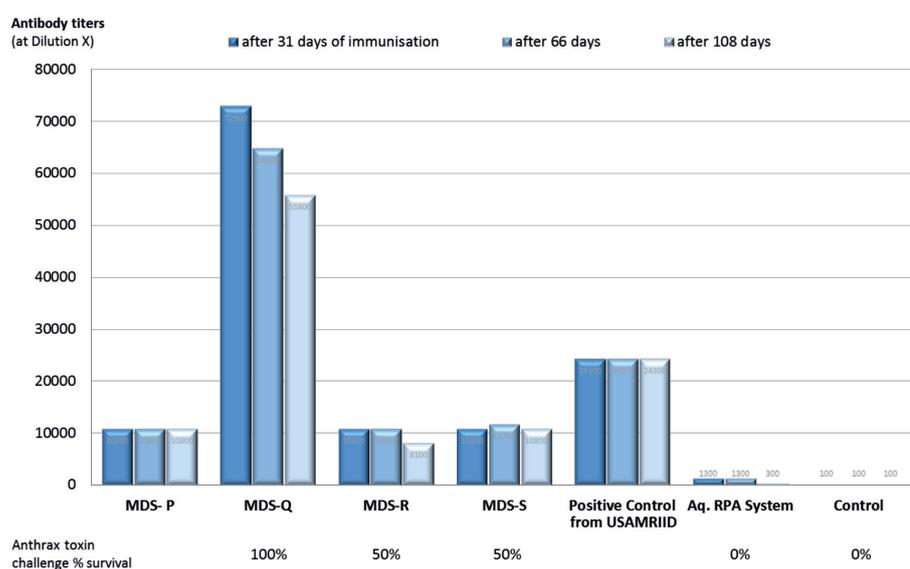


Figure 1: Efficacy of selected MDSs in mice via two-dose oral immunisation followed by anthrax toxin challenge.

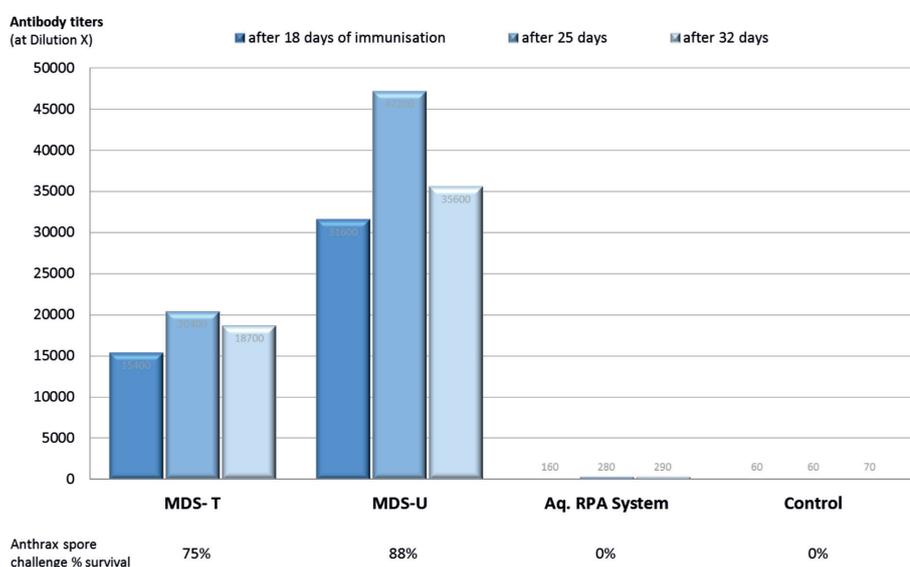


Figure 2: Efficacy of selected MDSs in rabbits via two-dose oral immunisation followed by live anthrax spore challenge.

### Immunisation of Mice with MDS via Two-Dose Oral Administration

We evaluated these MDSs for their efficacy to elicit immune response in mice. Figure 1 shows the antibody (IgG) titres in mice immunised with selected MDSs via two-dose oral administration. Mice immunised with selected MDS products were challenged with anthrax toxin. Figure 1 includes toxin challenge studies on selected MDSs via the oral-route against anthrax toxin.

Our orally delivered MDS-Q showed extremely high IgG titres throughout the 108-day testing period, exhibiting a two- to three-fold increase over the parenterally delivered positive control (and a 50-fold increase over the aqueous RPA system). Since the MDS-Q exhibited 70000 IgG titres 31 days after immunisation, it is very likely that the MDS-immunised mice were already fully protected within 31 days after two-dose oral immunisation. The IgG titres induced by the MDSs remained high over the testing period of 108 days, indicating a continuous controlled or pulsatile release of the RPA and ADJ over that period.

In the anthrax toxin challenge studies, all control (non-immunised) mice died within the first three days, demonstrating that the challenge was correctly administered to the mice. Aqueous RPA system group mice had 0% survival (all died within four days), while the MDS-R and MDS-S groups each showed 50% protection. Our MDS-Q group showed 100% survival and protection against the anthrax toxin challenge on the 42nd day when the experiments were terminated.

### Immunisation of Rabbits with MDS via Two-Dose Oral Administration

The MDSs were then tested for their efficacy to induce an antibody response in rabbits. Only selective MDS systems showing high efficacy in rabbit studies are reported here. Figure 2 shows the antibody titres in rabbits immunised with selected MDSs via two-dose oral administration. Rabbits immunised with selected MDS products were challenged after 42 days with live anthrax spores. Figure 2 includes the summary of the results of live anthrax spore challenge studies on rabbits.

These MDS systems produced high antibody titres in rabbits over the testing period of 18-32 days after the two-dose oral immunisation. Our MDS-U exhibited very high antibody titres in rabbits (35000-47000 during the 32-day testing

“This microsphere based delivery technology can be easily translated to the oral delivery of other proteins, peptides, vaccines and hormones.”

period), a 100-fold increase over the aqueous RPA system. The IgG titres induced by the MDSs remained high throughout the testing period indicating a continuous controlled (or pulsatile) release of the RPA and ADJ over the testing period. Since the MDS-U exhibited >45000 IgG titre 25 days after immunisation, it is likely that the MDS-immunised rabbits were already protected within those 25 days.

In the anthrax spore challenge studies, all control (non-immunised) rabbits died within the first four days, demonstrating that the challenge was correctly administered to the rabbits. The aqueous RPA system group also had no survival. Our MDS-T and MDS-U groups protected 75% and 88% of New Zealand White rabbits against live anthrax spores. Preliminary safety and histopathology studies indicated that the heart, lungs, liver, spleen, kidneys, and small intestine were normal in rabbits immunised with the delivery systems MDS-T and MDS-U and did not show any toxic effects.

These results from the mouse and rabbit studies indicate that we have successfully developed a viable oral delivery system for recombinant anthrax vaccine. By a two-dose oral administration, the MDS-Q afforded a 100% protection of mice against anthrax toxin and the MDS-U afforded an 88% protection of rabbits against live anthrax spores.

Given the high antibody titres and survival rate against exposure, our oral delivery system is approaching the same efficacy as parenteral delivery. The implications for this are enormous, especially as we begin to apply this platform to other vaccines, antigens, and hormones.

## CONCLUSION

PolyMicrospheres successfully developed a viable MDS offering effective oral delivery of recombinant anthrax vaccine. Our delivery system MDS-Q produced extremely high antibody titres (55000-72000 through 108 days) in mice, compared with the parenterally delivered positive control (24300 titres). In rabbits our delivery system MDS-U exhibited over 35000 antibody titres

through 32 days (a 100-fold increase over the aqueous RPA system), proving the value of a microsphere-based system. In addition our MDS-Q showed 100% protection in mice against lethal anthrax toxin challenge, while the aqueous RPA system was completely ineffective. Our MDS-U also protected 88% of rabbits against live anthrax spores whereas the aqueous RPA system again protected none. The IgG titres induced by the MDS systems remained high throughout the testing period indicating a continuous controlled (or pulsatile) release of the RPA and ADJ. Preliminary histopathology studies did not show any toxic effects.

Oral vaccination with an MDS was an immense advancement. Even the three week immunisation time with two doses of our MDS is a significant reduction from the current parenteral immunisation protocol requiring 3-4 doses of RPA-alum adjuvant spread over 18 months. The MDS delivery system protects its load against enzymatic degradation in the acidic environment of the stomach, and the bioadhesive properties of the microspheres increase the adhesion and residence time in the small intestine, thereby providing increased time to stimulate full immune response and protection against anthrax spores.

Oral vaccination with an MDS offers several key advantages over parenteral administration: it reduces immunisation time, can be self-administered, and can be packaged in a stable form as a pill (with a long shelf-life). On a macro level it simplifies the logistics of immunisation to large populations by increasing compliance and eliminating the need for medical personnel, thus increasing availability and lowering the system cost.

We are still optimising various parameters but are certainly moving in the right direction: towards the efficacious oral delivery of vaccines and other therapeutics. This microsphere-based delivery technology can be easily translated to the oral delivery of other proteins, peptides, vaccines and hormones. The societal implications are very exciting, as we are beginning thinking about clinical trials and delivering this to large populations.

## ACKNOWLEDGEMENT

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## MEETING THE CHALLENGES OF PAEDIATRIC DOSING

Although paediatric drugs are traditionally administered in a liquid formulation, recent studies have suggested that orally disintegrating mini-tablets may be a more accurate, convenient and less messy dosage form. Don Barbieri, Technical Support Manager at SPI Pharma, explores the benefits of this method and reviews two case studies looking at whether quality standards can be met and the importance of taste in paediatric formulations.

A widely held belief in paediatric drug administration is that liquids are easier for children to take. In reality however, administering an accurate liquid dose has always been, and continues to be, an issue. Liquids can be messy and spill, possibly reducing the efficacy of the medication should the child be under-dosed as a result.

Dose variability has been greatly reduced through the use of calibrated measuring devices, but successful dosing with these devices completely depends on the caregiver's ability to measure the dose accurately and consistently and the patient's willingness to take the medication. Other concerns in paediatric liquid dosing include:

- The need to refrigerate reconstituted suspensions to ensure stability over the course of treatment
- The possibility of microbial contamination
- The inclusion of excipients, such as preservatives, that are not required in solid dosage forms.

### NOVEL APPROACHES IN PAEDIATRIC DOSING

Recent studies have confirmed the preference of small tablets over syrups for children. Orally disintegrating mini-tablets (ODMTs) offer a promising alternative approach in paediatric dosing. This novel

“Orally disintegrating mini-tablets offer a promising alternative approach in paediatric dosing.”

dosage form offers accurate and precise weight-based dosing, dose titration, fast disintegration, and, perhaps, enhanced dissolution and pharmacokinetic profiles. Since they are designed to disintegrate in the oral cavity in approximately 10 seconds or less there is no need for water, an important consideration where sources of clean water are limited. When it comes to dosing convenience and improved compliance, ODMTs offer some distinct advantages over traditional tablets and liquids, even children as young as six months of age have been shown to be able to swallow ODMTs effectively.<sup>1, 2, 3</sup>

In addition to ODMTs, sub-lingual (SL) tablets and orally dispersible powders (ODPs) are good approaches to consider when designing a paediatric dosage form. In all of these formulation approaches it's important to remember that good taste, convenient dosing and improved swallowability are key elements in achieving successful paediatric dosing regimens and successful therapeutic outcomes. These patient-friendly dosage forms play a significant role in meeting these objectives.



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“Formulation of orally dispersible tablet and powder blends containing taste-masked multi-particulates is not without its challenges.”

### ENHANCING PALATABILITY

Taste and mouthfeel are, of course, also major considerations in palatability. If the dosage doesn't have good mouthfeel, has an unpleasant odour and/or a bitter taste there is a reduced likelihood that the child will consume the medication. Therefore, taste masking of bitter actives is of the utmost importance. In many cases this can be achieved through the proper selection of flavours and sweeteners. In other cases however, taste masking can only be achieved through the application of an aqueous gelatin coating (e.g. Actimask®, SPI Pharma) to active drug particles or by the application of a functional polymer coat to active coated multi-particulates to produce multi-unit pellet system (MUPS) beads. Selection of the most appropriate taste-masking system and excipients is critical to ensure acceptable palatability and therefore patient acceptance.

### CONSIDERATIONS FOR ORALLY DISPERSIBLE DOSAGE FORMS

Functionally coated MUPS multi-particulates are probably not a good fit for use with mini- or sublingual tablets and would be better formulated into more standard dosage forms. MUPS particles

can be fairly large (approximately 300-400 µm), which increases the risk of blend and tablet non-uniformity, especially when compressing mini-tablets at very low weights. Consequently orally dispersible powders packaged in stick packs or sachets and standard size chewable or orally disintegrating tablets may be better options when formulating with MUPS-type systems, making them more suitable for use with older paediatric patients who can swallow or chew tablets.

Active drug particles coacervated with gelatin are also not a good fit for use with mini or sublingual tablets for the same blend and tablet non-uniformity and dosing concerns noted above. They are more appropriately used with standard-sized orally disintegrating or chewable tablets and orally dispersible powders or granules. Coacervated gelatin products are intended for direct administration into the oral cavity. They have a smooth mouthfeel and good palatability, making them ideal candidates for use with these dosage forms.

Formulation of orally dispersible tablet and powder blends containing taste-masked multi-particulates is not without its challenges. As is typical in most blending processes, particle size of the excipients, along with the particle size of the actives, must be comparable in size and density to ensure good blend and content uniformities. The use of “off-the-shelf”, co-processed drug delivery platforms and excipients (e.g. SPI Pharma's Pharmaburst® 500 for orally disintegrating tablets, Compressol® SM and Advantol® 300 for chewable tablets, and Pharmasperse® 416 for orally dispersible powders) can facilitate formulation efforts and possibly increase a product's speed to market.

### CASE STUDIES IN PAEDIATRIC DOSING

Two case studies that summarise practical approaches in paediatric formulation development follow:

**1. Meeting Quality Standards & Demonstrating Proof of Concept in ODMTs**  
ODMTs of approximately 10 to 12 mg are typically compressed to a tablet with a diameter of approximately 3 mm. The intention of the study was to demonstrate the feasibility of formulating orally disintegrating mini-tablets using a co-processed off-the-shelf drug delivery platform (Pharmaburst 500, SPI Pharma) to address the challenges of meeting content uniformity and other quality requirements in such small tablets.

Phenylephrine HCl and dextromethorphan HBr – two active pharmaceutical ingredients (APIs) used extensively in paediatric liquid formulations – were utilised as model drugs in separate trials. In both trials the active was 25% of the formulation composition, the co-processed system comprised approximately 65% and the balance of the formulation consisted of sweeteners, flavours, a flow aid (colloidal silicon dioxide) and a lubricant (Lubripharm® – sodium stearyl fumarate). Taste-masking was achieved through the use of dry-blended flavours and sweeteners.

As with any dry-blend mixture, the order of mixing and identification of appropriate processing steps are critical. The formulators developed optimised blending procedures which included de-lumping/screening steps followed by ordered addition of the excipients and actives, and utilisation of appropriate blending steps and times.

Tablets were compressed to a total tablet weight of 10 mg using 2.5 mm multi-tip punches. In-process samples were tested and the tablets met accepted quality standards (Table 1).

Acceptance values (AV) of 5.2 and 7.1 were well below the limit of 15. Mini-tablet hardness results approximated 10 N, which helped to facilitate the rapid disintegration time of approximately two seconds, while the friability results of 0.3% and 0.8% indicated that tablets were sufficiently robust even at a low hardness.

The results of this proof of concept study demonstrate the feasibility of formulating ODMTs, using a commercially available drug delivery platform, that are intended

Test Performed	Trial 1 Phenylephrine HCl	Trial 2 Dextromethorphan HBr
Average Tablet Weight (mg)	10.0	10.1
Friability (%)	0.8	0.3
Hardness (N)	9	10
Disintegration (sec)	2.3	2.0
Assay (%)	103.3	99.0
Tablet Content Uniformity (Acceptance Value)	5.2	7.1

Table 1: Results from case study 1.

for administration to small children, possibly as young as six months of age. The applicability of this dosage form, however, could be limited to the use of lower dose actives that do not require taste masking or that can be taste masked using flavours and sweeteners.

## 2. The Importance of Taste Panel

### Evaluations to guide Formulation Decisions

A taste panel found two orally dispersible tablet formulations containing citrus flavours in combination with either citric or tartaric acid to have an unacceptable bitter taste, however formulations containing peppermint or menthol flavour had an acceptable taste without bitterness. The active drug particles were taste masked with a standard, reverse enteric polymer coating that solubilises at  $\text{pH} \leq 5$ . Upon further review, the hypothesis was that the acidic nature of the tablet formulation dissolved the taste-masking barrier while still in the mouth, rendering the polymer coating ineffective.

To test this hypothesis, tablets containing citric or tartaric acid, as well as tablets without an acid, were dissolved in about 20 mL of water and the pH of each tablet solution was determined. Tablets containing

an acid had a pH of approximately 4.3 whilst the tablets without an acidifying agent had a pH of approximately 8 or more. The solubility of the polymer coating at lower pH explains why bitterness was encountered in formulations containing an acid and not in those without. These findings, although expected and in no way surprising, stress the importance of using taste panel evaluations to help guide formulation decisions, increase patient acceptance and uncover potential organoleptic issues.

## CONCLUSION

Traditionally the use of liquid formulations has been the go-to dosage form in paediatrics; however, accurate dosing with liquids has always been and continues to be challenging. The use of orally dispersible, patient-friendly dosage forms including ODMTs, sublingual tablets, orally dispersible powders and others, in combination with appropriate taste masking, offers promising alternative approaches to liquids for effective and accurate paediatric dosing.

The use of commercially available, preformulated drug delivery platforms helps to address some of the challenges faced by formulators as they develop these

dosage forms, thereby facilitating product development and possibly increasing the speed of new patient-friendly paediatric products to market.

## ABOUT THE COMPANY

SPI Pharma provides innovative solutions to global pharmaceutical and nutritional customers, solving the most challenging formulation problems efficiently, cost-effectively and with a focus on service. Serving over 55 countries in the manufacture and marketing of antacid actives, excipients, drug delivery systems for tablets and powders, taste-masked actives and vaccine adjuvants, SPI Pharma employs over 300 people globally and is backed by parent company Associated British Foods (ABF) also specialising in drug development services, having participated in over 60 commercially launched and marketed drugs globally.

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## ABOUT THE AUTHOR

Don Barbieri has been with SPI Pharma since August of 2015 as the Technical Products Manager. He is responsible for managing SPI Pharma's excipient line and drug delivery platforms which include Mannogem® (mannitol), Actimask® (taste-masked APIs), Pharmaburst® 500, Advantol® 300 and the Pharmasperse® 416 product lines.

Mr Barbieri has worked in the pharmaceutical industry for over 30 years with responsibilities in a number of different areas including manufacturing, technical services, and process and formulation development. Prior to joining SPI Pharma in 2015, he was with Patheon in Cincinnati, OH, US, as the Associate Director of Formulation and Process Development.

Barbieri is a graduate of the Rutgers College of Pharmacy in (NJ, US) and is currently a registered pharmacist in New Jersey, Wisconsin and Pennsylvania.



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## ORALLY DISINTEGRATING FILMS FOR THE DELIVERY OF BIOTHERAPEUTICS & NANO / MICROPARTICLE FORMULATIONS

In this article, Carmen Popescu, PhD, Senior Project Co-ordinator, Roquette America, summarises the benefits and applications of orally dissolving film dosage forms, with claims supported by two case studies, one demonstrating the suitability of ODFs for the delivery of micro and nanoparticles, the other showing how this property of ODFs exhibits promise as a next-generation immunisation system.

Amongst patient-centric drug delivery systems designed to increase compliance in specific patient populations (paediatric, geriatric and psychiatric patients, and those with dysphagia, for example) orally dissolving films (ODFs) are preferred to classic dosage forms. Principally, this is due to their ease of administration without water (allowing portability, they can be taken “on the go”) and their pleasant taste and mouth feel – making them as much a “treat” as a treatment.

“This platform provides a non-invasive alternative to IV administration while producing excellent dose content uniformity and rapid dissolution performance. The ability to avoid first-pass metabolism makes ODF a very attractive delivery system, especially for paediatric and geriatric populations.”

The main pharmaceutical appeal of ODFs as a class of drug delivery system resides in the fact that they can deliver the drug directly to the systemic circulation (avoiding first-pass metabolism). ODFs inherently provide for lower doses, thereby enhancing drug efficacy, improving the onset of action, and consequently patient compliance. Manufacturer’s attraction for these dosage forms resides in improved lifecycle management, market differentiation, innovation and brand creation.

In recent years, pharmaceutical companies are focusing their attention on continuous processing and ODFs are very good candidates when processed by hot melt extrusion (HME).

### ODF FORMULATION REQUIREMENTS

Usually the film strip size is 2x3 cm at 30-40 mg weight and loaded with and 20-30 mg active pharmaceutical ingredient (API). The composition requires:

- A film forming polymer or combinations of polymers (e.g. starches, maltodextrins, pullulan, gelatine, cellulosic derivatives (HPMC), alginate, carrageenan, gums, etc)
- A plasticiser (e.g. sorbitol, glycerol, triacetin or propylene glycol)



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- A sweetening agent
- A flavouring agent
- A colouring agent
- A surfactant, depending on formulation particulars
- A saliva stimulating agent.

### BEST API CANDIDATES FOR ODF FORMULATION

Hydrosoluble and ethanol-soluble APIs are ideal candidates at a low dose of 5-30% w/w of the dry substance in the formula, meaning less than 30 mg/day dosing. Highly potent drugs and those prone to first-pass metabolism can be delivered at low doses in ODFs. Recently (as in the case studies that follow) nano/micronised BCS class II and IV drugs and biomolecules have also been identified as suitable candidates for ODF delivery, replacing an injectable form with an oral one by selecting film forming polymers with suitable rheological properties.

### WHAT PROCESSES ARE AVAILABLE FOR MANUFACTURING ODFS?

Commonly used methods in the industry are:

- Solvent casting
- Hot melt extrusion (HME)<sup>1</sup>
- Solid dispersion
- Semisolid casting
- Rolling.

In recent years 2D and 3D printing methods are making rapid progress by facilitating the translation of ODFs from patient-centric to truly personalised medicine.

A major challenge in ODF formulation is excipients screening which must be done in order to find the right balance between disintegration time, rheological properties, API stability and mouth feel (see case studies that follow) while minimising the number of ingredients. It is better to handle just one polymer rather than a combination of polymers.

### CASE STUDY 1: ODF FOR BENZOCAINE MICRO / NANOPARTICLE DELIVERY

Micronisation and nanonisation are methods used to increase the aqueous solubility of BCS class II and IV drugs. Traditionally, nanoparticles are delivered by the intravenous route, meaning patient compliance is impaired. We found that ODFs are a very good oral delivery alternative for nano and microparticles

Sample ID	Strip mass	Benzocaine mass/strip	Benzocaine concentration
	mg (SD)	mg (SD)	w/w% (SD)
Micro	80.8 (10.7)	10.4 (1.9)	12.9 (0.5)
Nano	53.2 (1.4)	4.0 (0.1)	7.5 (0.2)

Table 1: Benzocaine ODF drug content uniformity.

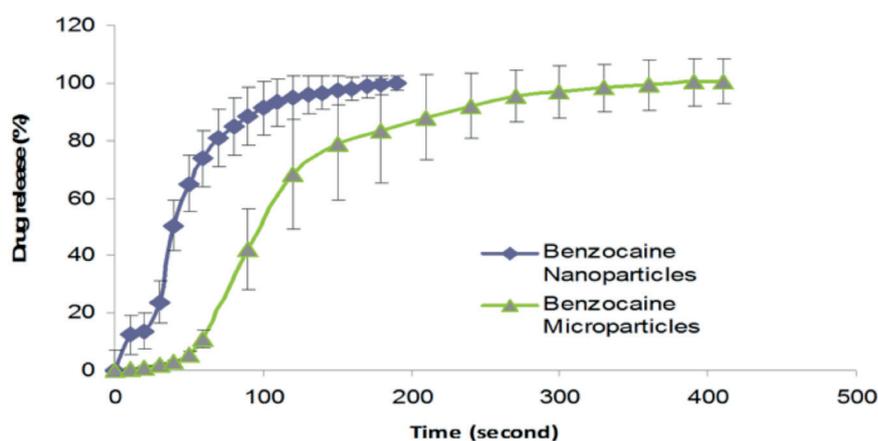


Figure 1: Benzocaine ODF Dissolution.

due to the convenience of administration, dose uniformity and physical stability.

Using Roquette's single, non-GMO pre-gelatinised hydroxypropyl pea starch polymer, Lycoat® RS720, ODFs containing benzocaine as a model drug were prepared using a film casting technique at room temperature. Lycoat® RS720 dispersed easily in cold water within minutes without lump formation. It is able to form films without the need for organic solvents, and permits loading of API (benzocaine as a model drug) in crystalline form as micro/nanoparticles. Lycoat® RS720 has a neutral taste and colour.

#### Drug Content Uniformity

ODF strips were completely dissolved in 100 mL HCl pH 1.5 under sonication and then filtered through a 0.2 µm syringe filter. The drug concentration was evaluated by UV absorption at 226 nm, in triplicate, using a UV-Vis spectrometer Lambda 20 (Perkin Elmer, Waltham, MA, US). Both micro and nanoparticle strips exhibited good content uniformity as evidenced in the concentration standard deviation (Table 1).

#### Dissolution Evaluation

Simulated saliva consisted of a phosphate buffered saline solution (2.38 g Na<sub>2</sub>HPO<sub>4</sub>, 0.19 g KH<sub>2</sub>PO<sub>4</sub> and 8 g NaCl per litre of distilled water adjusted with phosphoric acid to pH 6.75). Dissolution profiles of

benzocaine ODFs were obtained using a DISTEK (Rainbow Dynamic Dissolution Monitor System coupled with Indigo data process software) in 500 mL of simulated saliva fluid at 37 ±0.5 °C with stirring at 100 rpm. Benzocaine ODFs were coupled with a pin and the dissolution process was progressed at the bottom of a vessel. The drug concentration was evaluated by UV absorbance at 282nm, in triplicate, using a UV-Vis spectrometer Lambda 20, Perkin Elmer (Figure 1).

#### Rheological Properties Evaluation

Young's modulus, tensile strength and elongation at break were determined using an INSTRON 4502 universal testing machine (Instron, Norwood, MA, US), equipped with two pneumatic grips. The ODFs were placed between the grips and tensile stress was applied at 50 mm/min until rupture (Table 2).

#### Powder X-ray diffraction (PXRD)

Data were collected using an X'Pert Pro MPD system (PANalytical, Almelo, the Netherlands) equipped with a copper anode (Kα = 1.5406 Å), programmable divergence slit and X'Celerator™ RTMS detector. The operational voltage and amperage were set to 45 kV and 40 mA, respectively.

Diffraction data were collected over a 2-60° 2θ at a step size of 0.0170° and an irradiation time of 31.75 seconds/step.

The benzocaine powder sample was back-filled into a stainless steel spinning sample holder, while the benzocaine ODF was placed into a zero-background stainless steel sample holder. PXRD data for Benzocaine ODF confirm the presence of crystalline API (Figure 2). Significant diffuse scattering over 2θ range is representative of polymer film matrix.

The Figure 2 inset shows the superimposition of benzocaine PXRD pattern (red) with film pattern (blue) indicating benzocaine diffraction peaks in the film pattern.

**Summary**

ODF technology is a classical dosage form which has been shown to be a novel vector for delivering micro and nanoparticles of BCS II and IV drugs. This platform provides a non-invasive alternative to IV administration while producing excellent dose content uniformity and rapid dissolution performance. The ability to avoid first-pass metabolism makes ODF a very attractive delivery system, especially for paediatric and geriatric populations.

**CASE STUDY 2: ODF BUCCAL MEASLES VACCINE FOR NEXT-GENERATION IMMUNISATION**

The buccal cavity possesses a rich source of antigen presenting cells (APCs) such as dendritic cells, which can be harnessed to immunise against infection. Immunisations using ODFs could be a very viable route in paediatrics.<sup>2</sup>

Live attenuated measles virus (antigen) and alum (adjuvant) were added to the solution (BSA crosslinking with glutaraldehyde) and spray dried using the Büchi Spray Dryer B-290 (Büchi, Flawil, Switzerland). Resulting microparticles (MP) were then incorporated in the ODF formulation based on Lycoat® RS720 film forming polymer (in presence of plasticiser) at room temperature under continuous mixing for 10-15 minutes until the suspension was uniformly dispersed.

The yield of the vaccine nanoparticles was 84.6% w/w with the size range (Malvern particle size analyser, Malvern Instruments, Malvern, UK) of 0.5-0.9 µm with a mean size of 0.67 µm. The half time of release, i.e. the time taken to release 50% of vaccine antigen from the nanoparticle, was seen to be about 12 hours. The rheological values of the vaccine loaded in oral disintegrating film (ODF) are summarised in Table 3.

	Thickness (mm)	Tensile strength (MPa)	Elongation at break (%)	Young modulus (MPa)
ODF placebo	0.098	12.8	2	575 +/-35
Benzocaine ODF	0.102	6.5	2	195 +/-60

Table 2: Benzocaine ODF rheological properties.

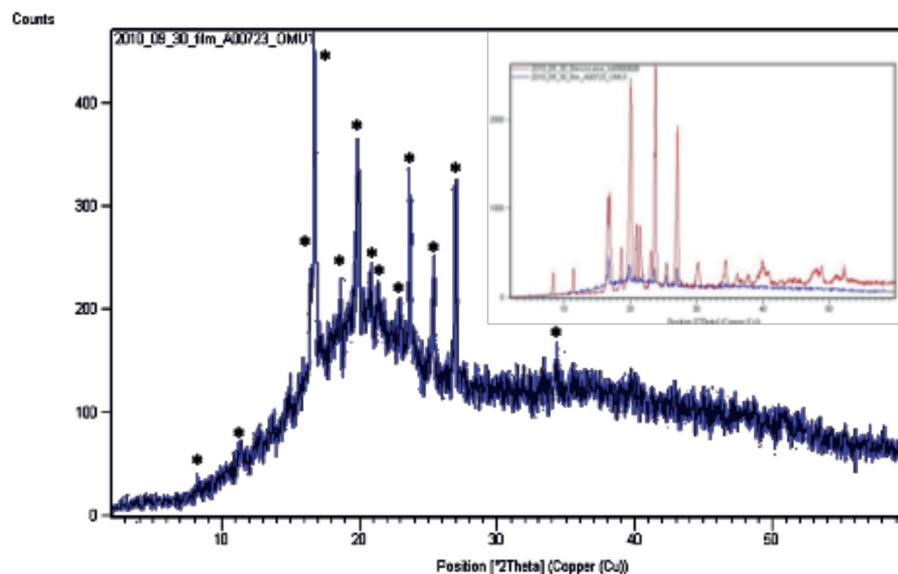


Figure 2: Benzocaine ODF powder X-ray diffraction.

	Tensile strength (MPa)	Young's Modulus (MPa)	% Elongation
Average	158	739	122
Deviation	24	192	4

Table 3: Measles vaccine nanoparticles ODF rheological properties.

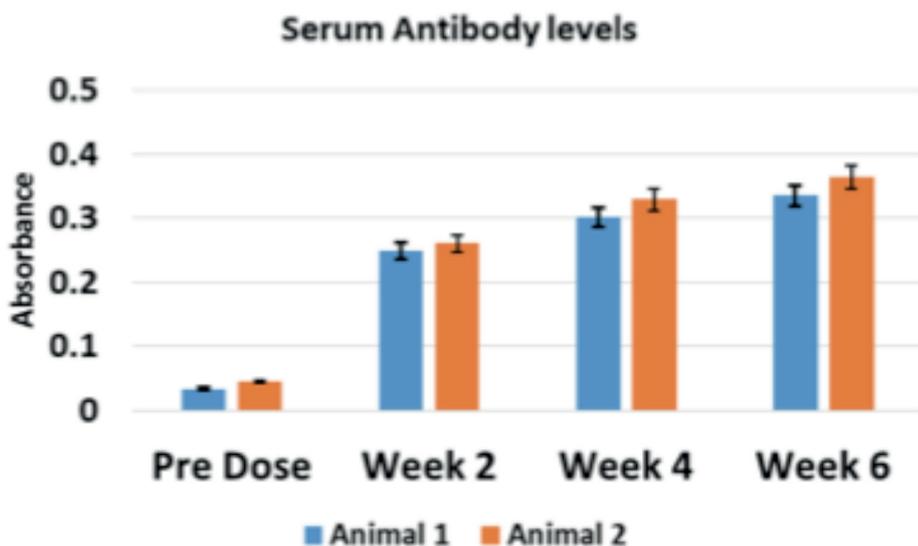


Figure 3: Serum antibody levels (n= 4). The serum antibody levels were measured using ELISA. There was a significant increase in the IgG level post dosing when compared with pre-dosing (P < 0.01).

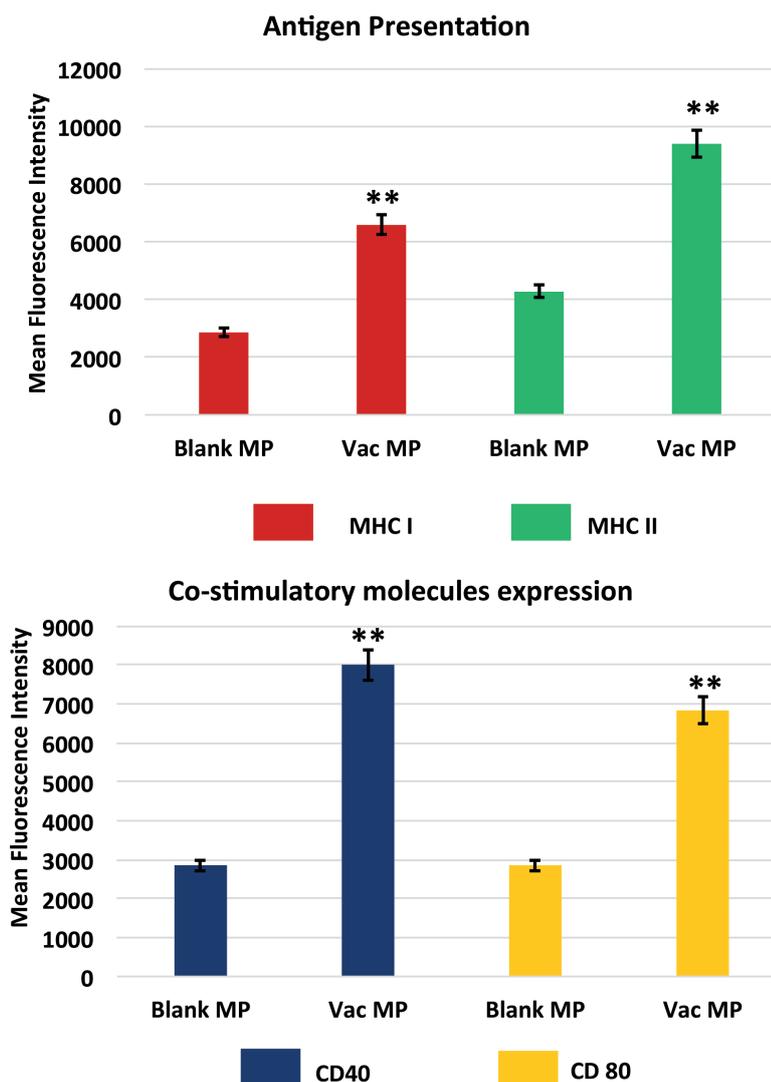


Figure 4: Antigen expression and co-stimulatory molecule expression on dendritic cells after exposure to the vaccine microparticles and blank microparticles (24 hrs.).

#### In Vivo Immunisation Results

The efficacy of the measles vaccine ODF was tested *in vivo* in two pigs by delivery via the buccal route. Blood serum samples were collected every two weeks and a specific ELISA was performed to quantify the amount of specific antibody present. The antibody titres from the *in vivo* immunisation studies are shown in Figure 3. There was a significant increase in the antibody level after weeks 2, 4 and 6, compared with pre-dose levels.

#### APCs and Co-Stimulatory Molecule Expression on Dendritic Cells

The antigen presentation is seen on either MHC I and II molecules. Along with this, there is a co-stimulation which is required for the APC to induce a Th1 or Th2 response. The dendritic cells were exposed to the vaccine microparticles for 24 hours and MHC I and II along with CD80 and CD40 (co-stimulatory molecules) were

measured using flow cytometry (Figure 4). There was a significant increase in antigen presentation and co-stimulatory molecule expression on the APCs.

#### Summary

Buccal delivery of ODFs loaded with vaccine nanoparticles is a promising immunisation system. Vaccine nanoparticles are better taken up by the antigen presenting cells

leading to further downstream process, generation of antibodies and thus creating an effective immunisation strategy. These encouraging preliminary results, will lead the way for further research in this area.

#### GIVING PRACTICALITY TO NOVELTY

It is well known that more than 45% of new drug entities have solubility issues and micronisation / nanonisation is one way to address this problem. However, micro- and nano-scaled drugs are usually delivered as injectables. Why an ODF? As shown in the above two case studies a good film former polymer can accommodate both hydrosoluble and insoluble (nano / microparticle) APIs of small and large molecules in an accurate dose, without changing their physical morphology (size, charge, crystallinity, etc). As the next generation of drugs belong to biopharmaceuticals, ODFs can be the best option for their oral delivery in order to increase patient compliance.

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