# ORAL PEPTIDE DELIVERY: TECHNOLOGY LANDSCAPE & CURRENT STATUS

In this review piece, Leila N Hassani, PhD, Scientist in the Novel Drug Delivery Technologies Group; Andy Lewis , PhD, Director of Novel Drug Delivery Technologies; and Joël Richard, PhD, Senior Vice-President, Peptides, all of Ipsen, provide an overview of the advantages provided, and challenges faced, by oral peptide delivery, and discuss the strengths and weaknesses of a selection of oral peptide technologies that are in advanced clinical development.

## INTRODUCTION

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

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Out of all of the available routes of administration, the oral route is the most preferred due to its convenience, patient friendliness and cost. However oral peptide delivery faces many hurdles such as poor absorption, poor permeability and rapid enzymatic or pH-induced degradation in the gastrointestinal tract.

Various approaches have been designed to overcome these barriers including absorption enhancers, conjugation or chemical modifications, enzyme inhibitors and mucoadhesive polymers, often in combination. Although for the most part, the obtained bioavailability remains very low, many of these approaches are showing promising results in clinical trials, with some products getting close to market.[1] Furthermore, there is still a need to propose enhanced approaches able to overcome issues encountered during oral peptide delivery such as food effects and intra-subject variability.

## PARTICULAR CONSIDERATIONS FOR ORAL PEPTIDE DELIVERY

### Pharmaceutics Considerations

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

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

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them better candidates for this route of administration. Furthermore the propensity of some peptides to self-assemble or aggregate adds an additional level of complexity to their delivery, as it would be expected that any such aggregates would be less likely to be absorbed, and strategies to prevent aggregation may need to be employed.

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

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

## PATHOPHYSIOLOGY, PHYSIOLOGY & PHARMACOLOGY CONSIDERATIONS

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

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

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

## END-USER CONSIDERATIONS

Prior to the development of an oral formulation, demographic factors including end-user age and culture should be considered. For example, in China it has been reported that there is a high prevalence of the use of the intravenous route,[2] the reasons for which are complex, but include patient perception of treatment efficacy.

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

Even if the oral route is the most preferred route of administration, safety and efficacy of the treatment by the patient is paramount over the route of delivery. For example, Flood et al evaluated the importance to patients of the product attributes of a nasal vaccine *versus* the injectable, and found that safety and efficacy were the most important and the route of delivery secondary.[3] It is therefore essential that safety and efficacy of any oral peptide formulation is maintained, in addition to any improvement in patient adherence.

## ANTICIPATING THE SWITCH INJECTABLE TO ORAL

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

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

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

## APPROACHES & STRATEGIES USED FOR ORAL PEPTIDE DELIVERY

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

The principle approaches consist of:

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

## ABSORPTION ENHANCERS

The oral absorption of a peptide can be improved by co-formulation with permeation enhancers that promote the crossing of the epithelial membrane involving the combination of several mechanisms, such as: (a) increased paracellular permeability by reversible opening of the tight junctions; this can be achieved for instance by fatty acids, toxins like *Zonula occludens toxin* (ZOT),[4] and chelating agents;[5] (b) increased transcellular permeation by increasing membrane fluidity, which can be achieved by a surfactant [6] or improving binding and uptake of the peptide by the epithelial cell and trafficking through the cell, e.g. using Fc-targeted

nanoparticles;[7] and (c) decreased mucus viscosity, e.g. using bile salts.[8]

Other excipients have been shown to improve permeability by bioadhesion, such as chitosan [9] and thiolated chitosan.[10] However, they are also suspected to exhibit tight-junction modifier properties, which means that their mechanism of action might not be fully understood.

Despite their proven efficacy, permeation enhancers may have potential toxic effects on the intestinal cells due to the high concentration needed in the formulation and their chronic use for long periods of treatment. This toxicity may result in membrane inflammation, membrane erosions and intestinal epithelium ulceration. In addition disrupting the lipid bilayer increases its permeability to drugs, but also to other pathogens which may result in infections and immunological reactions.[11] That said, the intestinal epithelium is actually relatively robust (*versus* the nasal epithelium, for example) and is constantly renewing itself, so any cellular damage is generally transient.

## PEPTIDASE INHIBITORS

Another key challenge in oral peptide delivery is to ensure their protection against the degradation induced by various types of endopeptidases (such as pepsin, trypsin, chymotrypsin, elastase) and exopeptidases (such as carboxypeptidases A and B). Agarwal *et al* reported the use of chicken and duck ovomucoids as enzyme inhibitors protecting insulin from trypsin and a-chymotrypsin digestion.[12] A Serine protease inhibitor, Serpin, can form covalent complexes with protease and thus protect peptides from peptidase attacks. Other studies demonstrated the potential of aprotinin and soybean trypsin inhibitors, camostat mesilate and chromostatin as enzyme inhibitors.

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

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

**Peptelligence®**

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

> "The capsules dissolve exposing the valve. Consequently, citric acid and sodium carbonate react together releasing carbon dioxide that inflates the balloon. As a result, the micro needles push into the intestinal wall"

Oral formulations of salmon calcitonin using Peptelligence® technology completed a randomised, double-blind, double-dummy, active- and placebo-controlled multiple-dose Phase III clinical trial in 565 post-menopausal osteoporotic patients.[13] It was found that the oral calcitonin formulation achieved improved efficacy *versus* the marketed nasal spray (i.e. greater increase in lumbar spine bone mineral density), probably due to the increased systemic peptide exposure.[14]

In addition, Peptelligence® was also used to develop an oral formulation of parathyroid hormone (PTH) that completed a Phase II clinical trial in osteoporosis compared with the reference injectable product on the market (Forteo®). It was shown that the pharmacokinetics were highly reproducible and oral PTH formulation increased bone density, although in this case efficacy was reduced compared with reference injectable treatment.[15]

## TRANSIENT PERMEATION ENHANCER

Chiasma, Inc (Newton, MA, US) is developing transient permeation enhancer (TPE) technology for the oral delivery of octreotide (Octreolin®). TPE technology is an enteric-coated liquid-filled capsule containing an oily suspension of the drug and sodium caprylate in hydrophilic microparticles that are mixed with castor oil or a medium-chain glyceride and/or caprylic acid. Sodium caprylate is claimed to provide a transient opening of the tight junctions providing enhanced paracellular peptide absorption. Chiasma completed Phase III clinical trials of oral octreotide (Octreolin®) using TPE technology. Chiasma claims that the TPE technology protects the peptide from enzymatic digestion and transiently opens tight junctions. It was demonstrated that an oral dose of 20 mg octreotide using TPE technology,[16] can achieve similar pharmacokinetics as 0.1mg octerotide SC (a relative oral bioavailability of less than 1%). It was also shown that bioactivity of the peptide is preserved, since the oral administration of octreotide led to the expected suppression of growth hormone (GH) secretion following a growth hormone-releasing-hormone (GHRH) induction test. However, food effects or drug-drug interactions were also observed: taking the Octreolin® capsule after a meal or with a proton pump inhibitor (like esomeprazole) led to gastric pH changes, significantly affecting oral absorption of the peptide.

In a multicentre Phase III clinical trial, 155 adults with acromegaly receiving injectable somatostatin analogs for three months were switched to oral Octreolin® containing 20 mg of octreotide twice-a-day and were evaluated for biochemical and symptomatic disease control for up to 13 months. Doses were escalated to 60 and then up to 80 mg/day to control insulin-like growth factor-1 (IGF-1). Once fixed the doses were maintained for a seven-month core treatment followed by a voluntary six-month period. Octreolin® demonstrated significant efficacy in controlling IGF-1 and GH concentrations for 13 months. In fact this efficacy was achieved in 65% of patients at the end of the core treatment period and in 62% patients at the end of the treatment. In addition, the effect was durable in 85% of the 91 patients initially controlled on oral Octreolin® with a sustained response for 13 months.[17] These results are comparable with those reported for 41 acromegaly patients responding to injectable octreotide LAR, 84% of these maintained baseline IGF-1/GH control at six months. In addition, during this study it was observed that the incidence of adverse events significantly decreased over time, suggesting that the safety profile of Octreolin® is consistent with the profile of injectable octreotide formulations.[17]

## MERRION'S GIPET® TECHNOLOGY

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

## ELIGEN® TECHNOLOGY

Emisphere Technologies (Roseland, NJ, US) has developed various types of oral formulations including solutions, tablets, and capsules, based on the Eligen® technology. This technology uses SNAC (sodium N-[8-(2-hydroxybenzoyl)amino] caprylate or salcaprozate sodium), 5-CNAC (N-(5-chlorosalicyloyl)-8-aminocaprylic acid), 4-CNAB (4-[(4-chloro-2-hydroxy- benzoyl)amino]butanoic acid) and SNAD (N-(10-[2-hydroxybenzoyl]-amino) decanoic acid) as absorption enhancers.

These excipients were claimed to form non-covalent complexes that protect them from digestive enzymes and improve the crossing of peptides and proteins trough the intestinal epithelium through a transcellular pathway. In addition, it was claimed that unlike the traditional penetration enhancers, SNACs do not cause histological damage to the intestinal epithelium. SNAC achieved generally recognised as safe (GRAS) status for its intended use in combination with nutrients added to food and dietary supplements.[19] Furthermore, the first product Eligen B12™ using SNAC in order to improve the absorption of vitamin B12 is now on the market.[20] Also, Eligen® technology completed Phase I clinical trials and has shown promising results for oral delivery of various peptides and proteins such as insulin, recombinant human growth hormone (rhGH), calcitonin and recombinant parathyroid hormone (rPTH).

## PROTEIN ORAL DELIVERY TECHNOLOGY POD™

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

## NOD TECHNOLOGY

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

## MIDATECH'S GOLD NANOPARTICLES

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

| Company | Lead Peptide | Technology Name | Technology composition | Formulation | Partnership | Current Stage of Development |
|---|---|---|---|---|---|---|
| Enteris Biopharma | Calcitonin | Peptelligence | Absorption enhancer (acyl carnitine) and enzyme inhibitor (organic acid: citric acid) | Tablet | Tarsa Therapeutics | Phase III |
| Chiasma | Octreotide | TPE | Suspension of drug particles in oils and abosorption enhancer (caprylic acid, C8, castor oil, medium chain) | Capsule | Roche (discontinued) | Phase III |
| Oramed | Insulin and exenatide | POD | Peptide with absorption enhancer (e.g.EDTA) and protease inhibitors ( e.g.soya bean tripsin inhibito, EDTA) enteric coated tablet/capsule | Capsule | Novartis | Phase II |
| Merrion pharmaceuticals | Insulin and GLP-1 analogues | GIPET | Absorption enhancer : medium chain fatty acids (sodium caprate) as a | Tablet | NovoNordisk | Phase I |
| Emisphere | Insulin and GLP-1 analogues | Eligen | Absorption enhancers SNAC, SNAD, 5-CNAC | Tablet | Novo Nordisk | Phase I & II |
| Nod Pharmaceuticals | Insulin | NOD | Bioadhesive calcium phosphate nanoparticles | Capsule | | Phase I |
| Midatech | Insulin and GLP-1 | GNP/Nanocells | Surface modified gold nanoparticles complexed with peptides | Adhesive buccal patch | | Phase I |
| Rani Therapeutics | Insulin and GLP 1 analogues | Robotic pill | Balloon-like structure outfitted with hollow micro needles made of sugar and preloaded with peptides. | Capsule made of biodegradable material (e.g. PLGA) | Novartis | Preclinical |

Figure 1: Table summarising selected oral peptide delivery technologies.

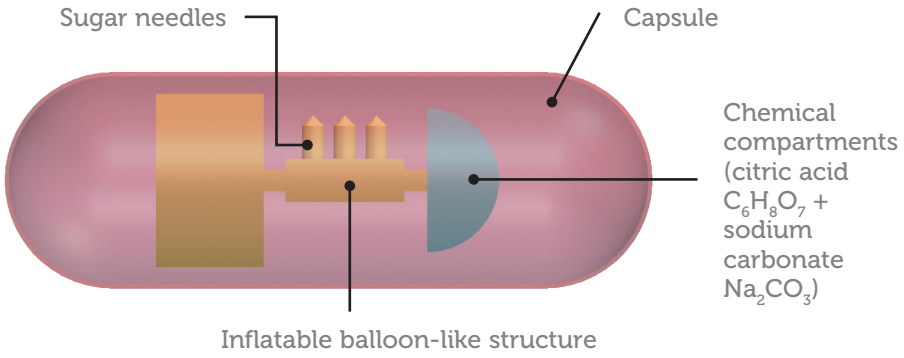


Figure 2: Schematic diagram of "robotic pill" concept comprising a capsule containing chemical compartments composed of citric acid and sodium carbonate in two chambers separated by a valve, and an inflatable balloon-like structure with hollow micro needles made of sugar and preloaded with the therapeutic peptide.

to deliver peptides via the buccal route, which avoids the outcomes encountered when delivering via the intestine. In fact, Gutniak *et al* showed that an adhesive buccal patch containing GPL-1 achieved a bioavailability in man of 47%.[23-24] In this way, Midatech developed a similar buccal patch delivering insulin from gold nanoparticles. This technology successfully completed Phase I in healthy volunteers and now is moving into a Phase II trial in patients.

## CONCLUSIONS

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

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

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

A very novel approach based on intra-enteral injection has been developed recently by Rani Therapeutics (San José, CA, US) for the oral delivery of large molecules including peptides, proteins and antibodies. It is called the "robotic pill" (see Figure 2) and consists of a capsule made of a biodegradable material (e.g. PLGA) which contains a valve separating citric acid and sodium carbonate in two chambers. This capsule includes a balloon-like structure containing hollow microneedles made of sugar and preloaded with peptides. Once in the intestine, dependent on pH level, the capsules dissolve exposing the valve. Consequently, citric acid and sodium carbonate react together releasing carbon dioxide that inflates the balloon. As a result, the micro needles push into the intestinal wall (intra-enteral injection), detach from the capsule and slowly dissolve. Preclinical studies showed very promising results and oral bioavailability over 50 %.[25]

Taken together the technologies and developments described here are likely to lead to a significant increase in the number of orally delivered peptides.

## ABOUT IPSEN

Ipsen is a global specialty-driven biotechnological group with total sales exceeding €1.2 billion (£850 million) in 2014. Ipsen sells more than 20 drugs in more than 115 countries, with a direct commercial presence in 30 countries.

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

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

## ABOUT THE AUTHORS

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Leila N Hassani, PhD, is a scientist in the Novel Drug Delivery Technologies group at Ipsen, acting as technology scout and scientific lead in projects applying innovative novel drug delivery technologies across the company's portfolio of peptides and biologics. Before joining Ipsen she earned her PhD in pharmaceutical technologies from the University of Angers, France, where she investigated protein and growth factors encapsulation using supercritical carbon dioxide process. Results generated from her research activities have been published in peer-reviewed journals.

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

**Joël Richard**
Joël Richard, PhD, has more than 25 years' experience in industrial R&D, including several global senior positions in various biotech and pharma companies. Dr Richard is currently Senior Vice-President, Peptides, at Ipsen. He is globally leading

all the CMC development activities of both injectable peptide products and oral small molecules, including APIs and drug products, with major franchises in Oncology, Endocrinology and Neurology. Dr Richard graduated from Ecole Normale Supérieure in Cachan, France. He gained a PhD in Materials Science from the University of Paris, France. In the last 15 years, Dr Richard has focused his research activity on new formulation and drug delivery technologies, especially for injectable protein and peptide formulations. Dr Richard has published 65 peer-reviewed scientific papers, eight book chapters and two review editorials in various fields (colloids and interfaces, drug delivery, supercritical fluids, protein formulations, sustained-release formulations etc). He is the author of more than 100 international communications and 53 patent families.

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