Challenges for Therapeutic Peptides Part 2: Delivery Systems

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The first part of this article (*IPT* 42, page 54) discussed some of the challenges facing peptides as a class of therapeutic agents and suggested that a more holistic approach that addressed bioavailability, stability, route of administration and cost of goods would improve the chances of success. In this second part, the authors turn their attention to novel drug delivery platforms and how these can add value to a peptide product – although ultimately it will be the health insurance companies that decide whether this 'added value' is worth paying for.

Keywords

Orally administered peptide
Intra/transdermal administration
Microelectronics/ microchip technology
Nasal Delivery
Bioavailability

Although peptide manufacturers are not normally involved with the formulation or delivery of the drug product, they are certainly aware that many of their clients opt at the start of development for delivery by injection, usually with very simple liquid formulations (water, saline or a standard excipient). Most peptides are not particularly stable in solution at ambient temperatures and must therefore be refrigerated, which – although acceptable in a hospital or a doctor's practice – is not convenient for self-medication or transport. Cold chain storage and transportation also significantly increases drug costs. That said, a number of peptides have been stabilised in solution using Generally Recognised as Safe (GRAS) and other pharmaceutically acceptable excipients, enabling storage at ambient temperatures. Arecor and Stabilitech are two examples of companies working in this field.

Not all peptides are readily soluble in standard injection solvents and, for those that are, highly concentrated solutions are often viscous requiring wide-bore needles, and are associated with local injection site reactions and non-compliance. Fluidcrystal (Camurus AB) or nanoparticle technology can dramatically reduce viscosity. The use of short, narrow-bore 31 or 32 gauge needles, such as those used on insulin pens, are essentially pain-free and daily injection may well be acceptable in contrast to once-weekly or once-monthly injection of more viscous formulations. New, more convenient and compliance-friendly injection devices for fluids are continually being developed.

Peptides can easily be prepared as solid formulations (by lyophilisation or spray drying) and these are almost invariably more stable than their liquid counterpart. However, this normally puts the onus of reconstitution in solution on the patient. There are also emergency situations (for example, glucagon in hypoglycaemia or use in the field) when there is little time or no second hand available for reconstitution of a powder. This makes direct injection of a stable, solid drug product formulation (such as Glide SDI technology) particularly attractive. There are many transdermal technologies as well as solid injection devices that permit the dosing of peptides as solids or dry coated microneedles (see Table 1). Such formulations are particularly applicable to poorly soluble peptides; however, their load may be limited to doses ≤1 mg to a maximum of 10 mg.

New Delivery Technologies

Alternative delivery platforms to needle injection are particularly attractive for peptides, and more new technologies are now in development than there is adequate funding to support. Platforms available for peptide therapeutics can be categorised by route of administration to include needle-free injection, intra/transdermal, intra-urethral, intravesical, intratracheal, nasal, oral, ocular, otic, pulmonary, pumps (external or implantable), topical, rectal and vaginal. Each of these platforms can be viewed as a regional administration

Table 1: Transdermal and oral delivery technologies for administering peptides

Intra- and transdermal delivery of peptides				
Company	**Details**	**Technology**	**Reports/Claims**	**Phase**
3M	Solid and hollow microneedle patches	sMTS, hMTS	hPTH, PTHrP	Pre, PI
Corium	Dissolvable peptide microneedle patch	MicroCor®	hPTH	PII
Isis Biopolymer	Iontophoresis	IsisIQ™	Collagen-stimulating peptides	Approved
NanoPass	Intradermal microneedle injection system	MicronJet	Proteins, vaccines	Approved
Pantech Biosolutions	Laser-assisted ablation	P.L.E.A.S.E.®	Triptorelin	PI
Phosphagenics	Topical	Targeted Penetration Matrix	Insulin	PII
Theraject	Dissolvable peptide microneedle patch	TheraJectMAT™	hPTH	PI
Vaxxas	Microprojection patch	Nanopatch	Vaccines	Pre
Vyteris	Iontophoresis	SmartPatch	Peptides	PII
Zosano	Solid coated microneedle patch	ZP Patch	hPTH	PII
Oral delivery of peptides				
Company	**Details**	**Technology**	**Reports/Claims**	**Phase**
Access	Oral, receptor-mediated uptake	CobOral®	Insulin, hGH	Pre
Aegis	Buccal, oral	Intravail®	AFPep, Octreotide	Pre
ArisGen	Buccal, oral	Ariscrown	Exendin, hPTH,Insulin	Pre
Biodel	Sublingual film tablet	VIAtab	Insulin	PI
Proxima Concepts	Oral, enteric-coated capsule	Axcess™	Calcitonin, hPTH	PII
Chiasma	Oral, oily suspension of enhancers	TPE Technology	Octreotide	PIII
Emisphere	Oral, passive transcellular uptake	Eligen®	Calcitonin, Insulin, GLP-1, PYY	PI-PIII
Merrion	Oral, enteric coated tablet	GIPET®	Insulin, GLP-1, GnRH Analog	PI
Midatech/Monosol	Buccal film, nanoparticles	PharmFilm	Insulin	PI
NanoMega Medical	Oral, nanoparticles		Insulin	Pre
NOD Pharmaceuticals	Oral, nanoparticles	NOD	Insulin	PI
Oramed	Oral, enteric coated tablet		Insulin, Exentatide	PII
Unigene	Oral, enteric coated tablet	Peptelligence®	Calcitonin, hPTH, CR845	PII-PIII

Data is from publicly available sources and is designed to give an overview of delivery technologies that have been tested with peptides. The list is intended to be reasonably comprehensive. It is assumed that platforms that can deliver vaccines or proteins can also deliver peptides. The status of clinical trials given represents the last reported status found in the public domain. Some will have progressed, but some will have been terminated.

route for the peptide to a target area, or as an alternative entry portal to avoid specific metabolic events (for example, hepatic first pass). They often enable flexible dosing as well as catering to specific patient populations. Currently, more focus is on intra/transdermal and oral delivery platforms. Future development of pulmonary platforms will probably depend much on the outcome of the approval process for Mannkind's inhalable insulin, Afrezza. A non exhaustive list of some of the oral and transdermal delivery technologies that have been developed for peptides is provided in Table 1. Although there are additional technologies we chose to limit the list to those that are in further stages of development or highly novel in their approach.

The focus on intra/transdermal administration reflects the ability of these technologies to deliver peptide (typically 40 to 100 per cent bioavailability versus subcutaneous injection) without the losses observed for many other alternative administration routes, as well as to provide highly accurate timing of the dose. Although most currently available devices have a limited load (≤10 mg), they are an exceptionally attractive platform for highly potent peptides (GLP-1 agonists, hPTH, calcitonin, and so on). The devices are based on diverse technologies:

- Those that create micropores in the skin allowing passive permeation of the peptide from a patch into the body ('poke and patch')
- Coated, hollow and channeled microneedle devices that puncture the skin to deliver the peptide ('coat and poke')
- Iontophoresis
- Topical enhancers
- Subcutaneous dissolvable implants

Microneedle devices or implants usually offer higher bioavailability and more consistent dosing. In some devices, the microneedles themselves are composed of the peptide in a biodegradable matrix.

> Transit rates through the gut are fast and subject to inter- and intra-patient variation, so release mechanisms that rely on environmental recognition are important. Some recent oral delivery technology platforms use the physical or biochemical environment of the gut lining to cause muco-adhesion to prolong release

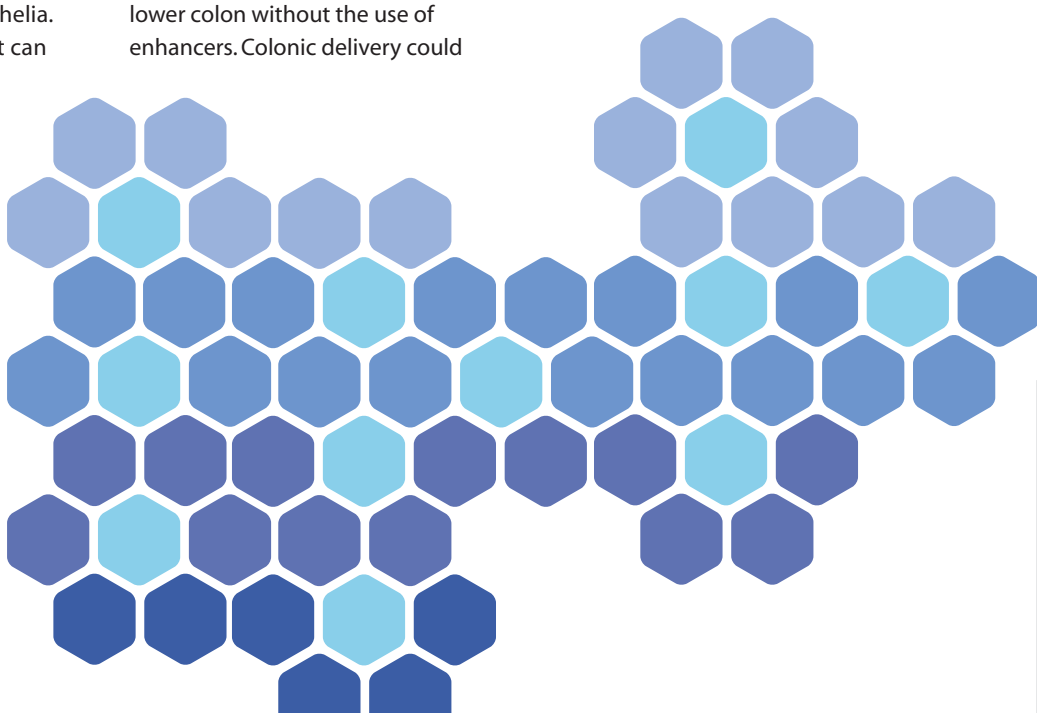
The 'Holy Grail'

Continued strong interest in oral administration (the 'holy grail' of peptide delivery) underscores the industry's desire to put peptide active pharmaceutical ingredients (APIs) into tablet or capsule form, and is seen as perhaps the last challenge before peptides become mainstream drugs. Oral administration of a tablet or capsule would be less expensive than injection if equivalent bioavailability could be achieved (currently not possible) and would be free of compliance issues. The gastrointestinal tract (in its broadest sense stretching from the oral cavity to the rectum) offers a wide range of specialised epithelia that peptides can traverse, but which differ in their morphology and their permeability, as well as their chemical and enzymatic environment. Proteolytic enzymes are found in the lumen of the intestine as well as in the brush border and epithelia. Microorganisms in the gut can also contribute to the proteolytic environment. Uptake into the body can be paracellular, transcellular, receptor-mediated or via the M-cells of Peyer's patches.

Almost all orally active peptide formulations use enhancers (such as salicylates, surfactants, fatty acids and derivatives, phospholipids, chelating agents, cyclodextrins, chitosan salts and derivatives, and so on) to support membrane permeation, although some peptides show intrinsic oral activity. At least one orally active peptide, linaclotide, exerts its activity by binding to extracellular receptors on the luminal surface of the intestine.

The final formulation for most orally administered peptides is a tablet or capsule with an enteric coating. Some also contain peptidase inhibitors. In 'best cases' up to 25 per cent bioavailability can be obtained, but it is often much lower. The main barrier is mucosal permeation, but hepatic first pass is another factor limiting bioavailability. The use of enhancers in the colon (no hepatic first pass) is precluded because of the risk of enhancing the uptake of pathogenic bacteria. There is evidence suggesting that some peptides (such as calcitonin) can be adsorbed readily from the lower colon without the use of enhancers. Colonic delivery could be easily achieved by suppository or less easily by oral colon delivery systems. Transit rates through the gut are fast and subject to inter and intra-patient variation, so release mechanisms that rely on environmental recognition are important. Some recent oral delivery technology platforms use the physical or biochemical environment of the gut lining to cause muco-adhesion to prolong release.

'Oral administration' also includes sublingual and buccal administration in the oral cavity. The buccal mucosa are non-keratinised and permeable to water, and buccal administration has been shown to be an effective delivery platform for some peptides. One example of a peptide that can be administered successfully in the oral cavity is Generex's RapidMist



Oral-lyn insulin product which is administered with an enhancer as finely dispersed droplets in the oral cavity.

No doubt new 'oral' platforms will become available. Some of these will use 'trojan horse' technologies, piggybacking peptides into the body using existing transport (such as PepT1) or receptor mechanisms. Access Pharmaceuticals has recently shown that nanoparticles coated with a Vitamin B12 analogue (Cobalamin) can use the intrinsic factor receptor in the ileum to transport proteins into the bloodstream by receptor-mediated endocytosis. The gut-associated lymphoid tissue (GALT) is capable of recognising and processing peptide antigens, and then taking these up into the lymphatic system. It is believed to be responsible for the action of the orally active peptide, B27PD, in treating uveitis.

Nasal Delivery

A number of clinical trials are studying peptides administered by nasal administration (for example, Aegis's Intravail or LMA's Vaxinator technology). This platform technology is enhancer-based, but has the advantage over oral intestinal delivery in that the mucosal environment is chemically and enzymatically more favourable. Bioavailability has been reported to be up to five per cent for desmopressin and salmon calcitonin. Nasal administration may also offer a direct route for peptides to reach the brain without confronting the blood-brain barrier. It is not certain whether the route is intraneuronal using olfactory neurons or extraneuronal by allowing diffusion directly into the subarachnoid space. Nasal administration also offers a quicker uptake route than most orals.

Currently, most delivery devices either release at a constant rate and/or can be controlled manually. As microelectronics/microchip technology advances into the field of drug delivery, the final goal will be to develop self-regulating delivery devices. MicroCHIPS Inc, for example, has developed a multi-chamber implantable chip that can deliver one or more peptide therapeutics by external computer control. Medimetrics has developed an oral capsule (IntelliCap) that, apart from releasing its drug load by internal pump on command, can monitor its own pH environment and position and report information back to an external computer. While the cost of introducing such devices for routine drug administration may remain prohibitive, they are exceptionally useful tools for shaping the form of future therapies.

Conclusion

A more holistic approach to developing peptide drugs would probably improve their acceptability and market success. However, decisions need to be made early in development. Alternative formulations do bring 'added value' in terms of patient convenience and compliance, as well as extending an existing drug's product life cycle. However, eventually it is the health insurance companies, in the US at least, that decide whether that 'added value' is affordable.

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