

Meeting the Challenges of Viable Delivery Systems for Peptide and Protein Pharmaceuticals

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Peptides and Proteins as Pharmaceuticals

Peptide and protein pharmaceuticals are different to conventional low molecular weight drugs; they are more challenging and complicated; they are often unstable, have large molecular weights and are polar in nature. The last two properties lead to poor permeability through biological membranes and consequently peptides and protein material are difficult to administer except by injection. Last but not least, the pattern of delivery required for clinical effect may be complex, i.e. pulsatile.

There is presently an urgent need to find new ways to deliver peptides and protein drugs and to control their absorption and distribution in the body. Uptake from the nose, lung and even the gastrointestinal tract are being considered as well as targeting to specific sites (organs and tissues). Peptides and proteins can be used for therapy as well as for prophylaxis (e.g. vaccines).

Delivery of Challenging Molecules

In a recent editorial, Rakesh Jain [1] stated that the delivery of therapeutics can be considered as the next frontier of molecular medicine. He commented that extraordinary advances in molecular biology and biotechnology have helped to identify novel targets and develop a vast array of therapeutic agents. However, (in his view), our understanding of the delivery of therapeutic agents has lagged behind. Similarly, in an editorial in Nature Biology in 1998 entitled "No pay off without delivery" [2], the importance of delivery was addressed. This editorial concluded that drug discovery is biotechnology's *raison d'être*, but its success is utterly dependent upon versatile delivery.

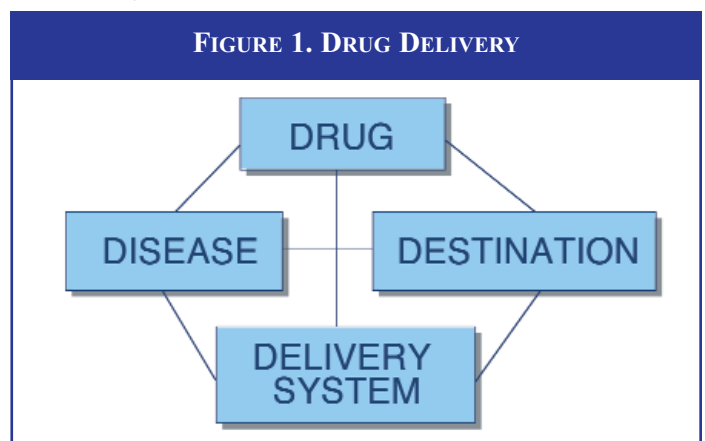
Enabling Technologies

In the past, when developing new products, drug delivery scientists have often employed delivery strategies to enhance an effect, such as in the development of a controlled release formulation. However, for the case of peptides and proteins, drug delivery can have a more critical role in enabling the development of a viable product. In so doing, a detailed knowledge of the properties of the compound needs to be integrated with delivery technology and the relevant aspects of patho/physiology and biology. Thus, certain key questions in drug delivery need to be considered early in the research and development process.

- What is required therapeutically?
- Is there a delivery problem?
- What technology is available?
- What is the scientific basis?
- Can it be achieved?
- If so, when?

The last question is often given too little attention. As many have learned to their cost, issues of scale-up, regulatory approval and time lines can be critical to commercial success.

The final design or choice of an appropriate delivery system will first require a proper consideration of three related issues; the properties of the drug; the disease and the destination in the body (figure 1). This approach can be viewed as "market pull" linked to an unmet medicine need. Unfortunately, many in the drug delivery field still adopt the alternative "technology push" approach. So-called novel or smart drug delivery systems are developed without proper understanding of clinical need or commercial reality. As a result, one finds examples of over-engineered delivery systems that have yet to "find" a drug or disease. Thus, in meeting the challenges of viable delivery systems for peptide and protein pharmaceuticals, one needs to consider not only viability itself but also the related aspects of credibility, attainability and reliability.



DRUG DELIVERY

TABLE 1. ROUTES OF ADMINISTRATION

- Parenteral
 - subcutaneous
 - intramuscular
 - intravenous
 - epidural
 - intrathecal
- Pulmonary
- Intranasal
- Oral
- Rectal
- Vaginal
- Buccal
- Sub-lingual
- Transdermal
- Ocular
- Esophageal

TABLE 2. ROUTES-RELATIVE DOSES FOR SAME PHARMACODYNAMIC EFFECT

i.v	1
s.c.	2
pulmonary	10
nasal	50
vaginal	200
rectal	500
oral	5000
Low molecular weight polypeptide- no additives	

When reviewing future opportunities for peptide and protein delivery, I usually have two key statements in mind. “Let the science win” and “Quality data in man.” Unfortunately, some of the so-called successes that have claimed for the improved delivery of peptides and proteins are hardly plausible scientifically and/or are based on limited preclinical data that will not extrapolate well to the clinical situation.

Delivery Routes

The choice of delivery routes for drugs is wide (table 1). The clinical application, drug properties, patient convenience, and required “performance” (e.g. bioavailability), are all key selection factors. For low molecular weight peptide drugs, the relative efficacies of different routes can be ranked for simple formulations (i.e. those without absorption enhancing additives) using i.v. administration as the control (table 2) [3]. Thus, for example, to obtain the same effect orally to that obtained by injection will require huge doses, and cost of goods and product reliability will be key factors.

Injectable Systems

While many groups are seeking non-injectable routes for peptide and protein delivery (e.g. pulmonary, oral, nasal), the inherent advantages of injectable systems need to be weighed against their disadvantages. Parenteral delivery can be used to target compounds to specific sites (via blood or lymphatic systems), as well as to provide precise pharmacokinetic and pharmacodynamic profiles. Exciting developments have shown how formulation technologies can be used to provide improved parenteral delivery (e.g. nanoparticles, liposomes, PEGylation) [4,5]. Engineering based systems, such as insulin pumps and injection pen systems (for insulin and human growth hormone (h-GH), have gained considerable success in the market. Needleless injection systems currently under development should have better patient acceptance [6]. These include systems employing liquid or powder technologies.

Polymer implants and microspheres based on poly(lactide-co-glycolide) (PLGA) have been very successful clinically [7]. However, polymer microspheres are not without problems in terms of loading, drug stability and release profiles. Processing, particularly sterilization, remains an issue. Table 3 lists some of the opportunities for improving the performance and production of polymer microspheres. New implant systems based on alternative concepts are currently under investigation including an implantable titanium device [8].

Non-injectable Delivery Systems: Pulmonary

A variety of transmucosal routes is currently being assessed for the

improved delivery of biopharmaceutical agents. Patton [9] has claimed that the lung is a logical target for non-invasive drug delivery. It should provide rapid onset of action and a variety of delivery devices (MDI, DPI, nebulizers). Good absorption, even of polar drugs, can be achieved, if the drug is delivered to the deep lung. Good patient compliance is to be expected provided that the device and delivery system are properly engineered. Similarly, good reliability should also be attainable. Understandably, insulin has been the molecule of choice and a number of different companies are pursuing novel pulmonary delivery systems using liquid and powder systems. Reported bioavailabilities, versus s.c. injection, range from 10-20% and reliability would appear to be as good as or better than for injectable insulin (s.c.). The various products are now in Phase II/Phase III clinical evaluation and the results look to be encouraging. However, some concerns over safety (lung function, cough) and increased antibody levels have been raised recently, but it is likely that inhaled products for insulin (and other therapeutic peptides) will reach the market soon. One great advantage of the lung is that it is possible to obtain reasonable absorption (i.e. 50% of the dose delivered) across the mucosal surfaces of the deep lung-alveolar region using simple formulations. It is therefore surprising that some groups are attempting to increase pulmonary absorption using enhancing materials such as phospholipids, surfactants and even bile salts [11].

Nasal

The nose is an alternative part of the respiratory system that can well be used for the delivery of therapeutic peptides and proteins (as well as vaccines). Nasal products for peptide delivery are on the market albeit with low bioavailability [12]. Nasal delivery can provide rapid onset of action and good deposition can be achieved readily for both liquid and powder systems. However, using simple formulations, the absorption of biopharmaceuticals from the nose of animal models and man is low (less than 1%). Therefore, in order to improve reliability and to address cost of goods issues, absorption promoters may be required. Various materials have been studied over the years. While many are effective, most are associated with problems of irritation and regulatory acceptance [13]. Often an increase in absorption (e.g. bioavailability) is associated with a direct effect of membrane damage (figure 2). However, some materials such as certain phospholipids can provide good absorption with low toxicity. Recently, we have discovered that the polysaccharide material chitosan, (derived from chitin by a process of selective deacetylation), can provide increased drug absorption with no evidence of toxic manifestations [14]. Both liquid and powder systems have been evaluated in animal models and in man (figure 3). Chitosan is believed to gain its effect through two processes, both related to its inherent positive charge. Chitosan is a bioadhesive material and therefore slows

DRUG DELIVERY

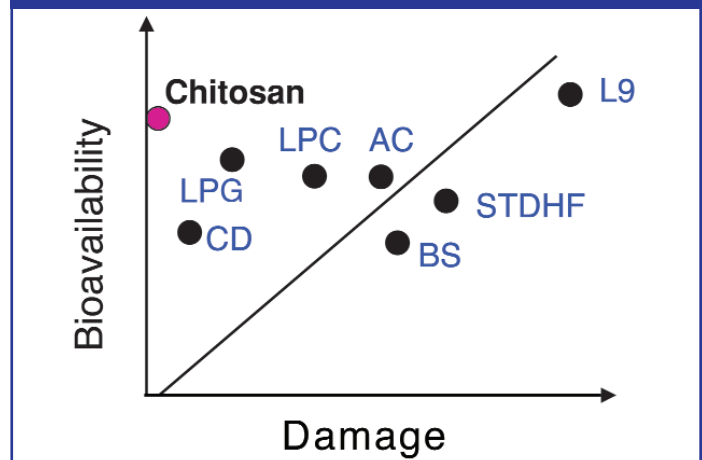
TABLE 3. POLYMER MICROSPHERES

- Change polymer
 - polyanhydrides
 - polycaprolactone
 - polyphosphazenes
 - etc.
- Add formulation agents
 - PEG
 - surfactants
 - Zn⁺⁺
 - complexing agents
 - antacids
 - sugar
 - etc.
- Change process
 - double emulsion
 - spray drying
 - phase separation
 - super-critical fluids

mucociliary clearance allowing more time for the therapeutic material to be absorbed. More importantly, chitosan can affect the tight junctions between cells. There is a transient and reversible effect whereby the tight junctions open to allow the passage of peptides [15]. Chitosan-based systems are also effective in enhancing the efficacy of nasal vaccines. Clinical trials have demonstrated that influenza (trivalent) and diphtheria toxin (CRM-197) can be delivered nasally with good effect [16].

One question often raised with nasal delivery is the question of the effect of colds and rhinitis. This may be important when delivering critical drugs such as insulin but for other drugs, no deleterious effects could be found. For example, Larsen et al. concluded that intranasal application of the low molecular weight polypeptide busserelin, represented a reliable mode of administration and that modification in administration route or a change in dosage schedule during naturally occurring nasal inflammation such as common cold and allergic rhinitis was unnecessary in patients undergoing chronic treatment [17].

FIGURE 2. THE RELATION BETWEEN PENETRATION ENHANCING EFFECT AND MEMBRANE DAMAGE.



The nasal route also provides a unique delivery opportunity. The olfactory region of the nose can be exploited to provide direct delivery of drugs into the brain [18]. Recent studies by Frey et al. [19] have demonstrated that polypeptide materials such as nerve growth factor can reach the CSF and brain tissues. In addition, exciting clinical studies by Fehm and Born [20], employing measurements of evoked potentials, have demonstrated that materials such as arginine vasopressin, angiotensin II, and insulin can be transported from nose to brain in man, in low quantities. This could be a novel way to avoid the blood-brain barrier and to provide a novel means of access to the brain.

Sublingual/Buccal:

The mouth has been examined as a delivery route for biopharmaceuticals by various groups using animal models and also in man. The pivotal clinical studies of de Groot and colleagues [21] using sublingual oxytocin suggest a low bioavailability of less than 1%. Therefore, the

FIGURE 3. THE NASAL ADMINISTRATION OF INSULIN TO THE SHEEP MODEL USING A 0.5% CHITOSAN SOLUTION AND A SALINE CONTROL.

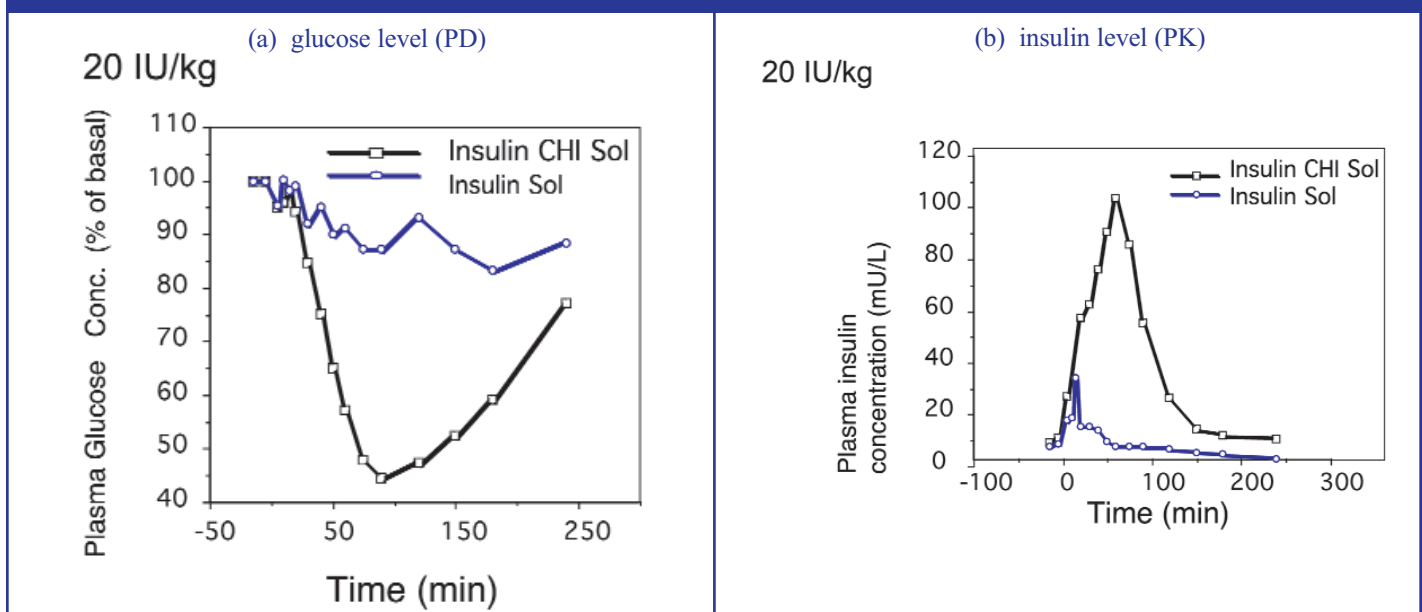


TABLE 4. PEPTIDE TRANSPORTERS

-‘drug smugglers’ ‘Trojan Peptides’

- Short peptide sequences identified with membrane translocation activity

- Antennapedia (penetratins)
- Fibroblast growth factor
- Galparan (transportan)
- HSV-1 structural protein -VP22
- HIV-Nuclear Transcription Activator Protein -Tat

9 interlinked amino acids, Tat 49....57 and peptoid analogs

results recently reported on the buccal administration of insulin using a spray device (MDI) are both surprising and potentially exciting. Reported clinical studies in diabetic subjects have demonstrated good efficacy with bioavailabilities in the range 5-10% [22]. The presence of undefined proprietary enhancing agents in the formulation could be a reason for the good permeation.

Transdermal:

The transdermal delivery of polypeptides has been evaluated by many different groups, but the results so far are not encouraging [23]. Good results in animal models do not translate well to man (usually because the chosen animal model has little relevance to the human skin). The skin of man provides a good barrier. Novel approaches to “driving” polypeptides across the skin, such as iontophoresis and ultrasound, have been explored but clinical results have been disappointing [24,25]. Insulin is an interesting case where physiological pH is a problem when considering iontophoresis. The charge on the molecule changes with pH gradient across the skin. Under electrophoresis, the molecule can be forced into the skin; but, as the pH changes as one moves from the skin surface to tissue, the charge on the molecule reverses and the molecule is forced back out!

A novel transdermal system using “transferosomes” (ultraflexible liposomes with low pore resistance) has been proposed by Cevc [26]. It is claimed that the system can transport therapeutic amounts of insulin across intact mammalian skin but detailed clinical results are awaited. Alternative engineering approaches, such as microneedles produced by photolithography, could well provide a more reliable transdermal system [27].

Oral

The holy grail of peptide and protein delivery is oral delivery. This field has been the subject of many attempts, particularly with insulin; but, as yet, few oral polypeptide products have reached the market.

When considering the oral delivery of therapeutics, it is important to first define the problem(s) and then to think about methods by which they can be overcome. Peptides and proteins are inherently unstable in the harsh conditions of the gastrointestinal tract (pH, enzymes, adsorption to solids); but, even if instability can be avoided, good absorption is not guaranteed. The work of Drew et al. on octreotide is instructive [28]. Octreotide is a cyclic polypeptide (a somatostatin analogue) that is very stable even in the small intestines. When given to man as a simple solution, the bioavailability is 0.6%. This can increase to 3.3% using a non-ionic surfactant (polyoxyethylene 24-cholesterol ether).

Therefore, for oral absorption, it is important to be realistic about potential product performance. If stability is an issue, then enteric coating and enzyme inhibitors can be used [29]. Absorption can be improved by the judicious choice of a permeation enhancer that can improve transcellular or paracellular transport (see below). Also of importance is the selection of a preferential absorption site. The small intestine and large intestine have both advantages and disadvantages. Therefore, before developing a delivery strategy, it can be important to evaluate the absorption of a candidate biopharmaceutical. While cell culture models (CaCo-2) and animal models (rat, pig) can be useful, there is no better model than man. Today it is possible to deliver drugs into different regions of the human gastrointestinal tract using “smart” capsules [30]. This avoids the highly invasive method of intubation.

Various methods to increase the absorption of challenging molecules from the gastrointestinal tract can be listed. These include permeation enhancers such as surfactants, chitosan (and derivatives thereof), chelating agents, as well as carriers and complexation systems [31]. Some of these strategies use known pharmaceutical excipients (GRAS status) which can alter cell permeability, usually by modification of the paracellular pathway. Non-covalent complexation strategies have also been reported [32]. A recent Phase I clinical study with insulin and an enhancer has demonstrated encouraging results, with an early appearance of the drug in the blood stream and reduction in glucose levels. It will be interesting to see if these results are confirmed in diabetic patients where issues of gastric emptying and the presence of food in the stomach could well influence the results. The modification of peptides and proteins chemically by lipidization or the attachment of hydrophilic and hydrophobic polymeric functions has also been described [33,34]. Such modifications would seem to be advantageous and preliminary clinical results appear encouraging; but, in many reported studies, it is hard to ascertain the exact nature of the formulations used (mention is made of undeclared formulation additives that could have a permeation enhancing effect). Clearly, such modifications result in a new chemical entity and the associated regulatory issues. The covalent attachment of moieties that permit the biopharmaceutical to exploit biological transporters is also an active area of research [35,36] (table 4). Here again, there is the disadvantage of covalent chemistry, but these approaches could offer exciting opportunities in the exploitation of natural pathways. A recent report by Morris et al. [37] could open up new approaches. These authors found that a 21 residue peptide that had hydrophilic and hydrophobic regions forms stable non-covalent complexes with peptides and proteins. They were able to use this system to deliver a model protein (L-galactosidase) into various cell lines. The system was claimed to have low toxicity but as yet, no in vivo data have been reported.

Last and (least?), is the concept of using nanoparticles for the delivery of peptide and protein drugs into the systemic circulation from the gastrointestinal tract. It is well known that certain specialized cells (M-cells) in the gastrointestinal tract can take up and transport particles [38]. The size and surface properties of the particles are key factors. This process is important for the development of oral vaccine systems. However, the quantities of material transported are low, even with systems with specific surface markers that provide enhanced interaction between particles and cells. Our work, and that of others conducted in man [39], would suggest that particle uptake will result in less than 0.1% of the administered dose being sequestered. This could be sufficient for a beneficial immune response when developing an oral vaccine but will surely be of no benefit for the oral delivery of peptides. Reported results in the literature and trade press that claim to have achieved “large” quantities delivered in this way, would appear to be wishful thinking or related to the limitation of the animal model or unsophisticated methods of particle uptake.

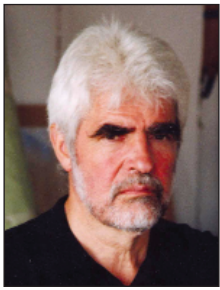
Conclusions

There are various methods available to the pharmaceutical scientist for the improved delivery of peptide and protein drugs. The choice will depend largely on clinical need and required performance specifications. In many cases, attention needs to be focussed both on aspects of quality as well as quantity. Small or moderate amounts (1-15%) of drug delivered safely and reliably to the systemic circulation could well be preferable to the delivery of larger amounts of drug (20-50%) that are delivered in an uncontrolled manner with a risk of adverse reactions. Any viable system will need to be developed with a sound scientific rationale. A key objective, so far as proof of principle is concerned, will be quality data obtained through studies in an appropriate animal model. In our thinking, the best animal model for man is man! ■

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DRUG DELIVERY



Professor SS (Bob) Davis obtained his Bachelors degree in Pharmacy from the School of Pharmacy at the University of London in 1964. He remained at the same University to study for a Ph.D. in colloid science (1967). In 1966, he was appointed Assistant Lecturer in Pharmaceutics and then to Lecturer in 1967. He was awarded his Doctor of Science degree (higher doctorate) in 1982. In 1968, he was awarded a one year Fulbright Scholarship to undertake postdoctoral studies with Professor Takeru Higuchi at the University of Kansas in the field of solution thermodynamics. In 1970, he moved to the University of Aston in Birmingham as Senior Lecturer and Head of the Pharmaceutics section. Here, he built up an active research group in drug delivery systems. Professor Davis took up his present position at Nottingham in 1975. He has run a large research group, studying novel drug delivery systems. Topics of research have included drug targeting (with particular emphasis on colloidal carriers), transmucosal delivery, oral and parenteral systems for controlled release and product evaluation through gamma scintigraphy. He has published over 700 papers and is co-editor of 7 books. He is the co-founder of two pharmaceutical companies, Danbiosyst (UK) Ltd. (now part of West Pharmaceutical Services) and Pharmaceutical Profiles Ltd. He has acted as a Consultant to various pharmaceutical companies and has served on numerous committees and panels, to include European Pharmacopoeia, Medicines Commission, and the Science & Engineering Research Council.