PSTT Vol. 2, No. 11 November 1999

Delivery of peptide and non-peptide drugs through the respiratory tract

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The respiratory tract, and the nose in particular, offers opportunities for improved drug delivery. Many drugs are rapidly and efficiently absorbed from the nasal cavity and, as a result, the nasal route may be used in crisis treatments (for example, for pain and nausea). Polar drugs, such as peptides and proteins, are not well absorbed across the nasal mucosa, unless they are delivered with an absorption enhancing material. Agents, such as the polysaccharide chitosan, that are able to open tight junctions between cells can offer important opportunities. The nasal route can also be used for the delivery of vaccines. This review makes a comparison between nasal and pulmonary delivery.

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▼ In the 1960s, a lecturer on lung and pulmonary delivery claimed that 'we are about to enter a new age of drug administration, where the lung will be used as a route to deliver a wide variety of drugs into the circulation'. It is now hoped that the lung could soon be used not only for the administration of drugs for local treatments but also for the delivery of biotechnology products, such as peptides and proteins, as well as conventional molecules such as analgesic agents. Certainly, up until the present time, drug delivery to the lung has largely been the domain of local treatments for asthma, respiratory diseases and infections. The use of the lung for systemic drug delivery has, in the main, been restricted to the administration of anaesthetic gases and nicotine administration from cigarettes (or drugs of abuse administered via smoking or inhalation techniques).

This review will consider recent advances in the delivery of drugs to the respiratory system for improved systemic uptake. It will concentrate on the nasal administration of drugs, such as peptides and proteins, and non-peptide compounds, many of which are either difficult to administer by other routes, or require a faster onset of action or other advantage. The advantages and disadvantages of nasal administration will be considered and a comparison made with pulmonary delivery.

The nose

The nose has been used for the systemic administration of drugs since ancient times. It remains a popular route for the administration of drugs of abuse such as cocaine, and in earlier times it was a favoured route for the administration of tobacco in the form of snuff. Although the surface area of the nose is not as large as that found in the lung, it does provide an effective site for the efficient systemic absorption of many conventional drugs, and particularly those compounds that are relatively water soluble but also lipophilic in nature (as shown by their partitioning properties)[1]. The nose is well vascularized and drugs absorbed from the nasal cavity will pass directly into the blood, without passing through the liver, where they would suffer from first-pass metabolism. The nose does contain metabolic enzymes; however, it has been found that degradation of compounds within the nasal lumen or in nasal tissues is not normally a problem that limits systemic appearance. Compounds that are normally difficult to deliver orally, for example those with a high first-pass effect such as propranolol and steroids, are often well absorbed from the nasal cavity without the need for sophisticated formulations and absorption enhancers. Nicotine provides an example of a drug that is well absorbed from the nasal cavity. Indeed, in many cases, with such lipophilic compounds, the pharmacokinetics are similar to those found after intravenous administration[2]. This means that the nose can be used in so called 'crisis treatments' for the rapid administration of compounds, such as in the treatment of pain, migraine, convulsions, seizures, sedation and

1461-5347/99/$ – see front matter PII: S1461-5347(99)00199-6

nausea. The use of nasal administration for conditions such as erectile dysfunction is also under consideration[3]. However, nasal absorption can be too rapid and a modification of the pharmacokinetic profiles can be achieved through the use of controlled release technologies such as microparticles and ion-exchange formulations.

On a commercial level, the nasal administration of migraine compounds has proved to be an effective and rapid way of providing pain relief[4]. Although some migraine compounds may be given orally, the onset of action can be slow. This is not only governed by the transit time for arrival of the drug at the absorption site in the intestines, but, in a large proportion of migraineurs, gastric stasis may mean that the drug does not arrive at its preferential site of absorption until two or more hours after oral administration. Such problems may be avoided with nasal formulations.

Physiological factors

When designing nasal products, it is worth considering some basic physiology. First, when a simple nasal formulation is placed in the nasal cavity (whether as a solution or powder), it will normally be cleared quite rapidly to the throat by a process of mucociliary clearance; the average half-time for clearance in man is approximately 15 minutes as measured by scintigraphic methods[5].

Moreover, it should be remembered that at any time, we predominantly use only one side of the nose for breathing. Essentially, one nostril is open (patent) while the other side is obstructed. A nasal cycle mechanism operates in switching a nostril from patency to obstructed, over a period of eight hours or so[6].

It is possible, through the use of bioadhesive and gelling formulations, to slow down the process of mucociliary clearance and retain a formulation within the nasal cavity for an extended period of time (in excess of three to four hours). This can be particularly useful for the administration of drugs required for local effect such as steroids, antihistamines, antiallergics and decongestants, but such strategies can also be used for the prolonged delivery of a drug into the systemic circulation, using a suitable controlled release formulation. Particular advantage can be gained through using bioadhesive powder systems in the form of starch or chitosan microspheres (Fig. 1)[7].

Irritation

As discussed above, some drugs can be well absorbed from the nasal cavity without the need for a specific delivery system. The main question with these compounds is often one of dose and the possibility of local irritation. Clearly, if a drug needs to be given at large dose, such as 50 mg or more, the nasal route will probably be unsuitable. Some drugs, by their very nature or the concentrations used (hyper osmotic solutions) can cause irritation in the nasal cavity. However, it is possible, through formulation options, such as the use of cyclodextrins and other complexation procedures, to minimize the irritation effects[8]. The measurement of irritation itself in non-human tests can present experimental challenges. If a compound is irritant through a mechanism of gross cell damage, then it is possible to screen for such effects in cell cultures, such as CaCO-2, or in animal models[9]. However, some compounds may be totally non-damaging but have irritant effects. Tolerance may be an important factor. Nicotine is a good example of this problem, where irritation occurs but the effect is transient and tolerance is soon obtained. The measurement of non-damaging irritation can be achieved in animal models using techniques such as the measurement of evoked potential or the measurement of

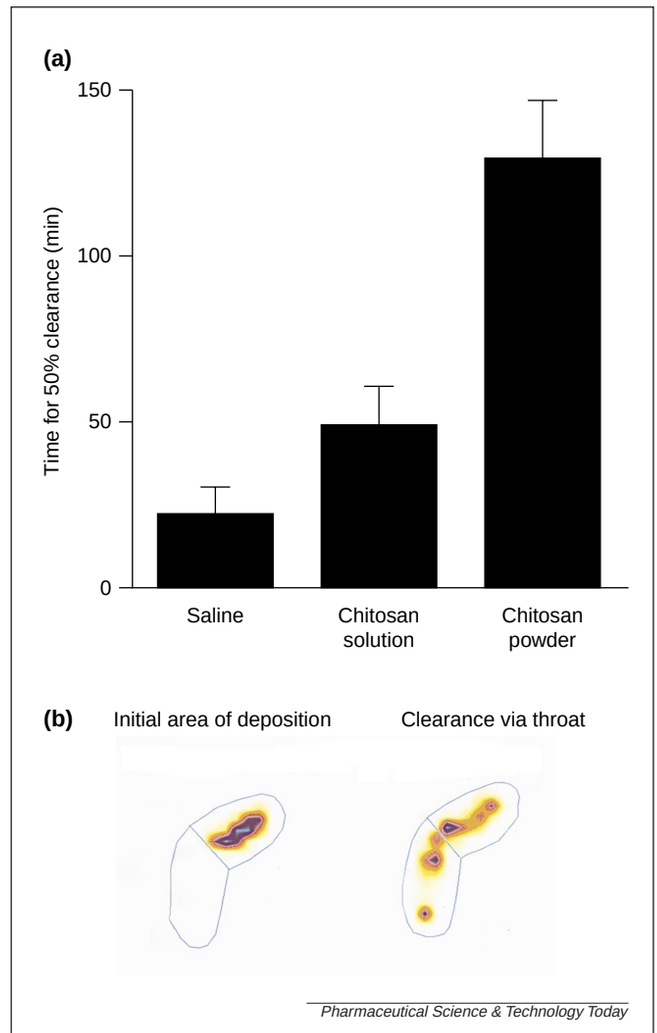

Figure 1. (a) Clearance of chitosan formulations from the nasal cavity of human subjects using gamma scintigraphy; (n = 8), label = technetium-99m. **(b)** Scintigraphic images showing deposition of formulation in the nasal cavity and clearance to the throat region.

immunocytochemical markers such as C-FOS protein[10]. Such studies can be performed as a prelude to the 'best' test for irritation, dose escalation studies in panels of human subjects.

Polar molecules and enhancers (peptides and proteins)

Despite the large surface area available in the nose and other features such as a lack of first-pass metabolism, the absorption of polar drugs from the nose is not normally good. For example, for peptide compounds such as parathyroid hormone (PTH), growth hormone, insulin, calcitonin and desmopressin, the bioavailability (rate and extent of absorption) from the nasal cavity of man is generally approximately 1% or less. This low uptake may be adequate for the development of some commercial products (such as desmopressin and calcitonin), because they have a wide therapeutic index and a relatively low 'cost of goods', but it may be necessary to use novel formulation strategies in order to produce a product with an absorption that can provide sufficient reliability in dosing (insulin), or an acceptable cost of goods for commercial viability.

It is well appreciated that it is possible to improve the transport of drugs across the nasal mucosa (and other mucous membranes) by using enhancer systems (Table 1). Unfortunately, with many of these systems that are largely based on surfactants, improvement in absorption is at the expense of tissue damage. Indeed, recent studies performed in Japan and the United States would suggest that, almost invariably, the high bioavailabilities achieved with absorption enhancers for the delivery of polar compounds across mucosal membranes can be associated with tissue damage[11]. Hence, a key goal in formulation development for nasal products is an ability to provide high bioavailability with minimum or no damage to the nasal mucosa. This can be achieved by using certain phospholipid compounds and, more particularly, cationic polymers such as chitosan[12].

Table 1. Nasal delivery–absorption enhancers

Class	Example	Mechanism
Chelators	EDTA	Opens tight junctions
Surfactants	Sodium dodecyl sulphate	Disrupts membrane
Bile salts and derivatives	Sodium deoxycholate	Opens tight junctions Disrupts membrane Enzyme inhibition Mucolytic
Fatty acid and derivatives	Oleic acid	Disrupts membrane
Enzyme inhibitors	Amastatin	Enzyme inhibition
Non-surfactants/ miscellaneous	Cyclodextrins N-acetyl cysteine	Disrupts membrane Mucolytic

Animal models

Before it is possible to test novel approaches to nasal delivery in man, it is necessary to perform initial experiments in animal models. The rat is a useful way of screening initial concepts but the standard model, as described by Hirai, can greatly overestimate the absorption that will occur in man[13]. One of the reasons for this is that the model does not permit normal mucociliary clearance function, and, moreover, the animal needs to be anaesthetized and it is known that certain anaesthetics can significantly increase the nasal absorption of polar molecules such as insulin[14]. The ovine model has a simple nasal architecture and can be used in a non-anaesthetized state and is also often predictive of results in man; not only qualitatively but also quantitatively, especially for peptides and proteins[14]. Although the shape of the ovine nose may be different to that of man, physiological processes, such as mucociliary clearance, are almost identical to those found in humans as assessed by the non-invasive technique of gamma scintigraphy. Recent studies on the clearance of gelling systems based upon polysaccharides (pectin and chitosan) have shown close correspondence between sheep and human data[5].

Absorption enhancers

Chitosan

Over recent years, the nasal delivery of challenging drugs, such as peptides and proteins and polar molecules such as morphine and migraine compounds has been greatly improved using an approach that is not based upon 'classical' surfactant enhancers, but upon a cationic polysaccharide called chitosan. Chitosan is deacetylated chitin, and chitin is the second most abundant polysaccharide in the world. Below a pH value of approximately 7.0, chitosan is water-soluble and, because of its cationic nature, can bind with mucosal surfaces and with mucin; the latter occurs through an interaction between the positively charged amine groups on the chitosan molecule and the negatively charged sialic acid groups on mucin. This interaction leads to bioadhesion and a reduced mucociliary clearance.

However, interestingly, chitosan has another and more dramatic effect in terms of providing improved nasal drug absorption. Chitosan can alter the paracellular transport of drugs by direct effect on the tight junctions between cells. It has been shown that the presence of chitosan at a mucosal surface can lead to a transient opening of the tight junctions, and this has been demonstrated in CaCO-2 studies, where measurements of transepithelial resistance, mannitol transport and histological measurements have been made[15]. The opening of the tight junctions occurs for a period of approximately 15 minutes and could allow molecules as large as growth hormone (20,000 Da) to pass from the nasal lumen into the circulation. For drugs with molecular weights below approximately 10,000 Da, the

use of chitosan can lead to an improvement in bioavailability of from 5–10-fold. It has been demonstrated that this chitosan effect with various polypeptides, that include desmopressin, insulin, leuprolide, calcitonin, PTH, CCK-8, as well as with polar compounds for the treatment of migraine, such as alniditan, and analgesic agents such as morphine. These studies have been performed in an ovine model and in man[4].

Chitosan is, by its very nature, a high molecular weight material that is not itself absorbed. Chitosan is non-toxic and has a reversible effect on ciliary function. Therefore, chitosan represents a new approach to improving the transmucosal delivery of challenging molecules. It has also been shown that the so-called chitosan effect of improving drug absorption across mucosal surfaces can be realized, not only in the nasal cavity but also in the gastrointestinal (GI) tract and vagina[15]. Modified chitosans that are soluble above pH 7 could be useful in the GI tract. Further improvement of drug absorption can be obtained by using powder formulations of chitosan, either as chitosan alone or in combination with gelatin in the form of microsphere systems. With some drugs, such as PTH, it is not possible to use liquid (chitosan) formulations of the drug because of stability problems, and thus powder formulations are essential. PTH formulations based on chitosan powder have performed well in the ovine model and in Phase I testing in human subjects. A representative example is shown in Fig. 2.

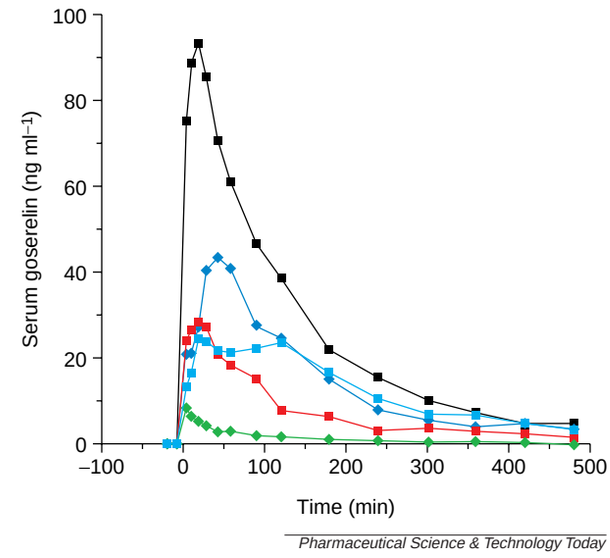

Figure 2. The chitosan effect as measured using a polypeptide (goserelin) in the sheep model (n = 4). Bioavailability versus subcutaneous ranges from 1.5% for simple solution formulation (no chitosan) to 37% with a chitosan powder system. CHI powder 1 (black); CHI powder 2 (blue); CHI solution (red); simple solution (green); subcutaneous (light blue). Reproduced, with permission, from L. Illum *et al.*, submitted.

Phospholipids

The nasal administration of large protein molecules, such as G-CSF and erythropoietin, can also be achieved via the nasal routes. However, not surprisingly, the quantities delivered will be less than those achieved for molecules of lower molecular weight, such as calcitonin and insulin. In general terms, the larger the molecule the less drug that can be safely and reliably delivered across the nasal mucosa using novel formulation. For these higher molecular weight polypeptides, phospholipid-based systems or combinations of phospholipid with chitosan or other bioadhesive materials have been shown to be effective, either in solution or as powder formulations (Fig. 3)[16].

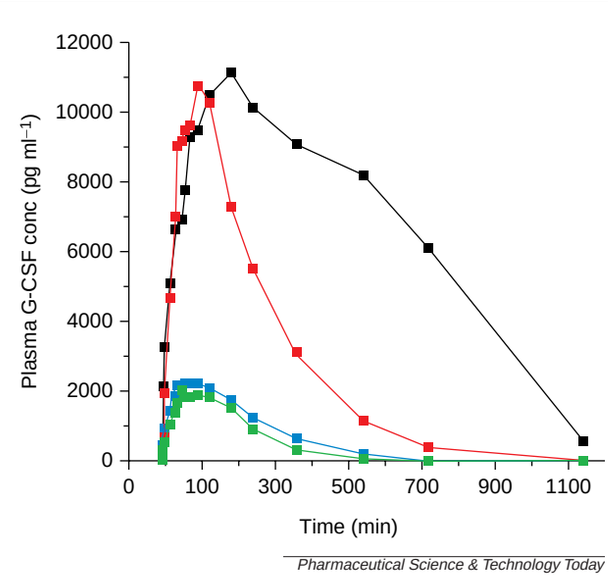

Figure 3. The use of a phospholipid, lysophosphatidyl-glycerol (LPG), to enhance the nasal absorption of G-CSF in the sheep model (n = 4). The protein was combined with starch microspheres (SMS), with LPG in solution, and as a mixture of LPG and SMS as a nasal powder. SC 10 μg kg^{-1} (black); SMS 40 μg kg^{-1} (blue); SMS + LPG 40 μg kg^{-1} (red); LPG 40 μg kg^{-1} (green).

Vaccines

The concept of improved delivery of a therapeutic agent via the nose by the transient modification of a paracellular-transport process can also be applied to the delivery of certain vaccine antigens. As the reader will appreciate, there is currently increasing interest in the use of the nose for mucosal vaccination. Such an approach is entirely sensible for prophylaxis against respiratory diseases, such as influenza, measles and RSV. Nasal administration of vaccines is itself an interesting area and space does not permit further detail here. Suffice to say that a

variety of vaccine systems, both liquid and particulate, is under current consideration.

As with any issue in drug delivery, the choice of the delivery system needs to take into account the properties of the drug or antigen, particularly its size, stability and physicochemical characteristics. The chitosan concept has been applied to several different antigens, to include those used for vaccines against influenza, whooping cough (*pertussis*) and other respiratory diseases. By the use of chitosan (in solution and powder form), it has been possible to obtain improved immune responses as measured in terms of antibody titres (IgG and IgA) as well as dramatic improvements in challenge tests in appropriate animal models[17].

Advantages of nasal delivery

The nose can be used for the delivery of several compounds, either because it affords rapid administration of the drug into the systemic circulation (without the need for injection) or permits the delivery of challenging molecules such as peptides and proteins, which are difficult to administer via routes other than by injection. The choice of a nasal delivery system will be dictated by the dose of the drug, the potential for irritation and precision of dosing. In our experience, and those of other groups, with the right type of delivery device and appropriate patient training, the nasal route of administration is able to provide equal or better precision of dosing compared with subcutaneous administration. This is far better than can be achieved through oral dosing or via the pulmonary route, unless one is using one of the more recently developed breath-activated or computer-controlled systems (see later). Total quantities of drug that can be given nasally will depend upon whether a liquid or powder formulation is being used. Normally, 150 μl is the maximum volume that can be applied at any one time into one nostril. For a powder formulation, the maximum quantity is approximately 50 mg, depending upon the bulk density of the material.

Reproducibility

The nasal administration of drugs can be relatively reliable and reproducible. Studies in man have shown that the coefficient of variation can be as good as or better than that achieved by subcutaneous administration. For example, Drejer *et al.*[18] reported that the intranasal administration of insulin in man resulted in a faster time course of absorption than subcutaneous injection with a significantly reduced inter-subject variation.

Nasal and pulmonary administration

The lung

The lung represents another part of the respiratory system that can be used for the effective delivery of drugs into the general circulation. For a long time, the lung has been used for the administration of drugs for the treatment of local conditions. However, more recently, spurred on by the advent of novel delivery devices, there is growing interest in the use of the lung for the systemic delivery of challenging molecules, such as peptides and proteins, as well as analgesic agents and even vaccines[19]. The lung can provide an excellent means for the rapid delivery of peptide drugs into the blood, providing that the drug can reach deeper regions. The large surface area of the lung is well known, although, interestingly, the permeability of the lung tissue in itself is not that different from other mucosal surfaces; it is the large area that provides for the rapid absorption. Small molecules, such as nicotine, and more polar species, such as morphine, are apparently relatively well absorbed from the central as well as the peripheral lungs. However, polypeptide molecules, such as insulin, are only well absorbed if they are delivered into the deep (alveolar) regions. Data from animal models would suggest that, for a typical polypeptide, 50% or more of the dose can be absorbed from the alveolar region. Thus, in contrast to the nose, the main issue in lung delivery is not one of improving absorption, but achieving drug delivery to the correct region of the lung.

Pulmonary delivery

In the field of nasal delivery, irrespective of whether one is using solution or a powder formulation, it is not difficult to deliver the whole dose into the nasal cavity. However, in the case of pulmonary delivery, the ability to deliver large quantities of drug selectively into the lung, and, more particularly, to the deep lung, presents problems. Scintigraphic data obtained in man would suggest that with conventional multidose inhaler systems and dry powder inhalers most of the drug does not reach the lung at all[20]. Some of the dose may be left in the device, some may be left in a spacer system (if used), but the majority impacts at the back of the throat and is then swallowed. For example, for a typical dry powder inhaler (DPI), one would expect approximately only 10–20% of the dose to reach the lung, and normally only half of this to reach the peripheral region. As discussed above, for a peptide molecule one would expect approximately only half of this dose, that reached the alveolar region, to be absorbed. A simple calculation indicates that for a conventional pulmonary delivery system, the probable achieved bioavailability, with reference to the original dose, will be relatively small (10% or less).

Importantly, some of the more recent concepts in delivery, in the form of dry powder systems and liquids, should permit larger quantities of drug to be delivered into the lung and, significantly, into the deep lung with greater dosing precision[21]. However, bioavailabilities for peptide drugs, even from an optimized dry powder system that provides good deposition in the lung, will range from 10–20%.

Insulin

Pulmonary delivery systems for the systemic administration of insulin are in an advanced stage of development and have been shown to perform well in Phase II investigations. It is probable that such delivery systems can also be applied to other appropriate peptide molecules, such as calcitonin and PTH, and perhaps even to larger species such as erythropoietin[22]. It should be remembered, however, that with some peptide therapeutics delivery to the lung may be inappropriate, simply because of the nature of the drug and its potential effect on lung tissues. Thus, growth factors, for example growth hormone and cytokines such as G-CSF, could be inappropriate for pulmonary delivery to man on such grounds, notwithstanding the fact that relatively good absorption could be obtained by using this route. It should also be appreciated that the lung has a large surface area and that local concentrations will be low, thereby minimizing any potential undesired effect.

As one would expect, pulmonary systems for insulin have been well received by patients who prefer this method of drug delivery to the normal process of injection. Importantly, Phase II studies have demonstrated that the product is well tolerated with no evidence of any effect on lung function over an extended period of time. Figure 4 contains data from recent studies on the use of hydroxyethyl starch microspheres in the delivery of insulin to the human lung using a 'conventional' DPI that provides good lung deposition[23].

Crisis treatment

In terms of the nose, the lung can be used for the rapid administration of drugs, particularly in the area of pain management. Morphine and Fentanyl appear to be good candidates, provided the drug itself does not cause local problems in the lung, such as bronchospasm. It would appear that inhalation systems – pulmonary or nasal – may soon be in development for cannabinoid delivery as part of a drive in the UK to establish whether these compounds could provide benefit in the treatment of pain and other conditions such as multiple sclerosis. It is clear that a molecule that can be delivered via the lung could also be delivered via the nose if an appropriate formulation strategy is used.

Comparison

The quantity of drug that can be delivered into the lung may be more limiting than that given nasally, but, of course, it is possible to give more than one dose. Table 2 offers a comparison of the relative merits of nasal, pulmonary and oral administration in terms of drug dosage. As would be expected, each route has its advantages and disadvantages. The final choice will depend on a variety of factors, but, in particular, the nature of the drug to be delivered, the dose of active material and the

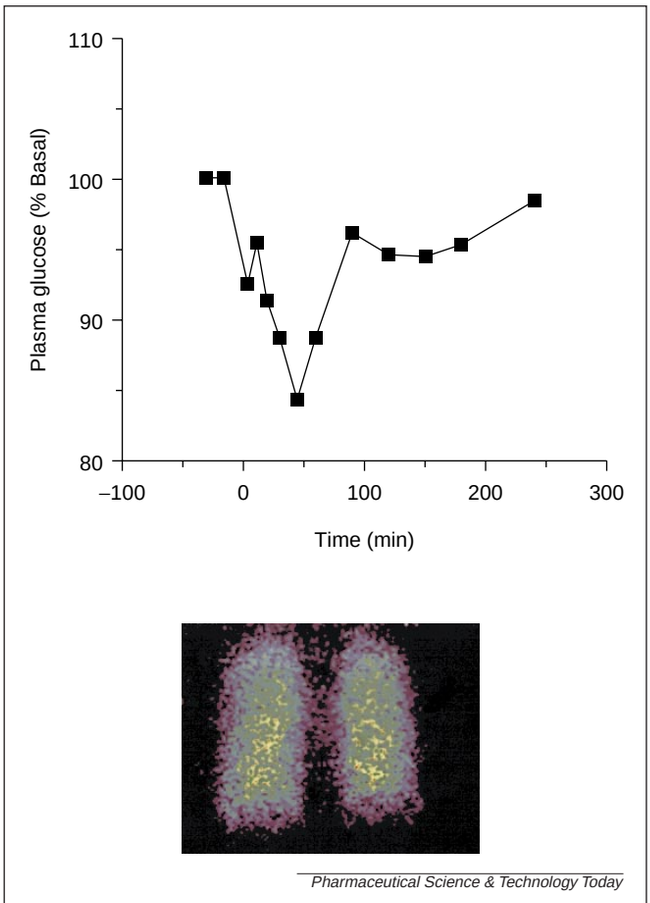

Figure 4. Effect of pulmonary administered insulin on plasma glucose levels in human subjects (n = 8), insulin dose = 25 i.u. Insulin incorporated into hydroxyethyl starch microspheres using spray drying. The administration device was a Valois Prohaler (Valois, Marly-Le-Roi, France). Formulations were labelled with technetium-99m to allow lung deposition to be followed (45% of estimated dose).

Table 2. A comparison of polypeptide delivery across mucosal surfaces

Route	Maximum dose (mg)	F (%)[a]	Amount delivered systemically (mg)
Oral (g.i.t.)	500	5	25
Lung (DPI)	5 × 3	12.5	2
Nasal – sol	30	25	7.5
– pdr	50	40	20

[a]Bioavailabilities that can be obtained using formulations acceptable for long-term human dosing.

nature of treatment (acute or chronic). Any decision over choice will also need to consider patient convenience and cost.

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