

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

of nasal administration will be compared with a comparison made with pulmonary delivery.

The nose

The nose has been used for the administration of drugs since ancient times. It is a popular route for the administration of drugs of abuse such as cocaine, and in the past it was a favoured route for the administration of tobacco in the form of snuff. Although the area of the nose is not as large as the surface of the lung, it does provide an effective route for the efficient systemic absorption of many drugs, and particularly those that are relatively water soluble and lipophilic in nature (as shown by their absorption properties)¹. The nose is well suited to the administration of drugs absorbed from the nasal cavity and pass directly into the blood, without having to pass through the liver, where they would be subject to first-pass metabolism. The nose also contains metabolic enzymes; however, it is not clear that degradation of compounds in the nasal lumen or in nasal tissues is not a major problem that limits systemic appearance of drugs that are normally difficult to deliver. For example those with a high first-pass effect, such as propranolol and steroids, are not well absorbed from the nasal cavity without sophisticated formulations and delivery systems. Nicotine provides an example of a drug that is well absorbed from the nasal cavity. Indeed, in many cases, with such drugs, the pharmacokinetics are similar to those found after intravenous administration. This means that the nose can be used for 'crisis treatments' for the rapid administration of compounds, such as in the treatment of migraine, convulsions, seizure

sorption 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 methods⁵.

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 so⁶.

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

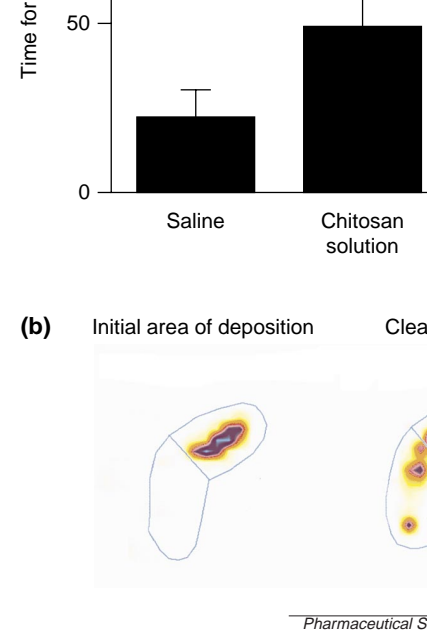


Figure 1. (a) Clearance of chitosan formulations in human subjects using gamma scintigraphy; (b) Scintigraphic images showing initial area of deposition and clearance to the throat.

irritation in the nasal cavity. However, there are various formulation options, such as the use of cyclodextrin complexation procedures, to minimize the irritation. The measurement of irritation itself in man is a present experimental challenge. If a compound is screened through a mechanism of gross cell damage, it is difficult to screen for such effects in cell cultures, so animal models⁹. However, some compounds are non-damaging but have irritant effects. Temperature is an important factor. Nicotine is a good example where irritation occurs but the effect is transient and is soon obtained. The measurement of non-irritation can be achieved in animal models using techniques such as measurement of evoked potential or the

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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 damage¹¹. 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 chitosan¹².

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 |

chitecture and can be used in a non-anaesthetic also often predictive of results in man; not only but also quantitatively, especially for peptides. Although the shape of the ovine nose may be different from that of man, physiological processes, such as mucociliary clearance, are almost identical to those found in human. The non-invasive technique of gamma scintigraphy has been used in studies on the clearance of gelling systems based on polysaccharides (pectin and chitosan) have shown a close correspondence between sheep and human data⁵.

Absorption enhancers

Chitosan

Over recent years, the nasal delivery of challenging drugs such as peptides and proteins and polar molecules such as migraine compounds has been greatly improved by the use of an approach that is not based upon 'classical' surfactant enhancers but upon a cationic polysaccharide called chitosan. Chitosan, or 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 positive charge, can bind with mucosal surfaces and with mucin. This 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 results in bioadhesion and a reduced mucociliary clearance.

However, interestingly, chitosan has another effect, a mucolytic effect in terms of providing improved nasal permeability. Chitosan can alter the paracellular transport of drugs by a direct effect on the tight junctions between cells. It has been shown that the presence of chitosan at a mucosal site can lead to a transient opening of the tight junctions between cells. This has been demonstrated in CaCO-2 studies, where nasal permeability transepithelial resistance, mannitol transport and mucin measurements have been made¹⁵. The opening of tight junctions occurs for a period of approximately 30 minutes and could allow molecules as large as growth hormone to pass from the nasal lumen into the circulation. Molecules with molecular weights below approximately 100,000 Da

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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 vagina¹⁵. 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.

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.

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

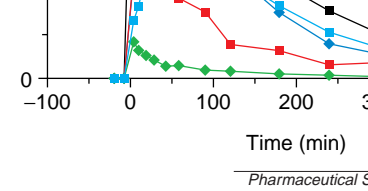


Figure 2. The chitosan effect as measured using a sheep model (goserelin) in the sheep model (n = 4). Bioavailability of goserelin subcutaneous ranges from 1.5% for simple solution to 37% with a chitosan powder system. Data series: simple solution (black); CHI powder 2 (blue); CHI solution (red); starch microspheres (green); subcutaneous (light blue). Reproduced, with permission, from L. Illum *et al.*, submitted.

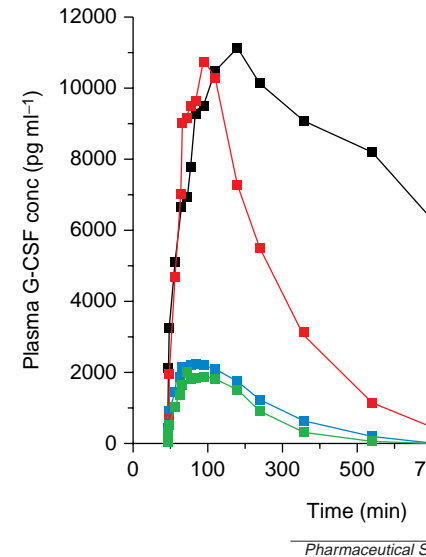


Figure 3. The use of a phospholipid, lysophosphatidylcholine, to enhance the nasal absorption of G-CSF in the sheep model. The protein was combined with starch microspheres (SMS) in solution, and as a mixture of LPG and SMS as a powder (SC). Data series: SC 10 µg kg⁻¹ (black); SMS 40 µg kg⁻¹ (blue); SC 40 µg kg⁻¹ (red); LPG 40 µg kg⁻¹ (green).

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dramatic improvements in challenge tests in appropriate animal models¹⁷.

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

surfaces; it is the large area that provides for the distribution. Small molecules, such as nicotine, and some species, such as morphine, are apparently readily absorbed from the central as well as the peripheral regions. However, polypeptide molecules, such as insulin, are not absorbed if they are delivered into the deep (alveolar) region. Data from animal models would suggest that for a polypeptide, 50% or more of the dose can be absorbed in the alveolar region. Thus, in contrast to the nose, the major advantage in lung delivery is not one of improving absorption, but of achieving drug delivery to the correct region of the lung.

Pulmonary delivery

In the field of nasal delivery, irrespective of whether a solution or a powder formulation, it is not difficult to deliver the whole dose into the nasal cavity. However, in pulmonary delivery, the ability to deliver large quantities of drug selectively into the lung, and, more particularly, to deliver drug to the peripheral region, presents problems. Scintigraphic data obtained in man suggest that with conventional multidose inhalers and dry powder inhalers most of the drug does not reach the peripheral region²⁰. Some of the dose may be left in the device or spacer, or left in a spacer system (if used), but the majority of the dose is back of the throat and is then swallowed. For example, with a typical dry powder inhaler (DPI), one would expect only 10–20% of the dose to reach the lung, and only about half of this to reach the peripheral region. As a result, for a peptide molecule one would expect approximately half of this dose, that reached the alveolar region, to be available. A simple calculation indicates that for a conventional multidose delivery system, the probable achieved bioavailability to the original dose, will be relatively small.

Importantly, some of the more recent concepts have been the form of dry powder systems and liquids that allow larger quantities of drug to be delivered into the peripheral region, significantly, into the deep lung with greater doses. However, bioavailabilities for peptide drugs, even with a modernized dry powder system that provides good delivery to the lung, will range from 10–20%.

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