sorbed 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 c comparison made with pulmona

The nose

The nose has been used for the istration of drugs since ancient t a popular route for the adminis of abuse such as cocaine, and in was a favoured route for the adm bacco in the form of snuff. Altho area of the nose is not as large the lung, it does provide an effe efficient systemic absorption o tional drugs, and particularly th that are relatively water so lipophilic in nature (as shown by ing properties)¹. The nose is w and drugs absorbed from the n pass directly into the blood, w through the liver, where they we first-pass metabolism. The nos metabolic enzymes; however, it that degradation of compounds lumen or in nasal tissues is not r lem that limits systemic appearan that are normally difficult to d example those with a high firstas propranolol and steroids, ar sorbed from the nasal cavity with sophisticated formulations and hancers. Nicotine provides an ex that is well absorbed from t Indeed, in many cases, with such pounds, the pharmacokinetics those found after intravenous a This means that the nose can be 'crisis treatments' for the rapid of compounds, such as in the tr migraine, convulsions, seizure

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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

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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 of human subjects using gamma scintigraphy; (n technetium-99m. (b) Scintigraphic images showin formulation in the nasal cavity and clearance to t

irritation in the nasal cavity. However, it formulation options, such as the use of cyc complexation procedures, to minimize th The measurement of irritation itself in n present experimental challenges. If a co through a mechanism of gross cell damage to screen for such effects in cell cultures, su animal models⁹. However, some compornon-damaging but have irritant effects. T important factor. Nicotine is a good exam where irritation occurs but the effect is trais soon obtained. The measurement of noncan be achieved in animal models using te measurement of evoked potential or th

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

also often predictive of results in man; not of but also quantitatively, especially for peptides Although the shape of the ovine nose may be of man, physiological processes, such as mucou are almost identical to those found in human the non-invasive technique of gamma scint studies on the clearance of gelling systems ba saccharides (pectin and chitosan) have shown dence between sheep and human data⁵.

chitecture and can be used in a non-anaesthet

Absorption enhancers Chitosan

Over recent years, the nasal delivery of challeng as peptides and proteins and polar molecules su and migraine compounds has been greatly imapproach that is not based upon 'classical' surfa but upon a cationic polysaccharide called chito deacetylated chitin, and chitin is the second polysaccharide in the world. Below a pH value of 7.0, chitosan is water-soluble and, because of ture, can bind with mucosal surfaces and with occurs through an interaction between the po amine groups on the chitosan molecule and charged sialic acid groups on mucin. This inter bioadhesion and a reduced mucociliary clearan

However, interestingly, chitosan has anothe matic effect in terms of providing improved nation. Chitosan can alter the paracellular transp direct effect on the tight junctions between of shown that the presence of chitosan at a muclead to a transient opening of the tight junction been demonstrated in CaCO-2 studies, where r transepithelial resistance, mannitol transport measurements have been made¹⁵. The openi junctions occurs for a period of approximately could allow molecules as large as growth hormore to pass from the nasal lumen into the circular with molecular weights below approximately

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of challenging molecules. It has also been shown that the socalled 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

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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 (goserelin) in the sheep model (n = 4). Bioavailat subcutaneous ranges from 1.5% for simple soluti chitosan) to 37% with a chitosan powder system (black); CHI powder 2 (blue); CHI solution (red); s (green); subcutaneous (light blue). Reproduced, w L Illum *et al.*, submitted.



Figure 3. The use of a phospholipid, lysophosphat to enhance the nasal absorption of G-CSF in the s The protein was combined with starch microsphe in solution, and as a mixture of LPG and SMS as a SC 10 μ g kg⁻¹ (black); SMS 40 μ g kg⁻¹ (blue); SI (red); LPG 40 μ g kg⁻¹ (green).

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 μ l 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 tion. Small molecules, such as nicotine, a species, such as morphine, are apparently relisorbed from the central as well as the per-However, polypeptide molecules, such as insulabsorbed if they are delivered into the deep (a Data from animal models would suggest the polypeptide, 50% or more of the dose can be the alveolar region. Thus, in contrast to the nose in lung delivery is not one of improving a achieving drug delivery to the correct region of

Pulmonary delivery

In the field of nasal delivery, irrespective of whe solution or a powder formulation, it is not diffic whole dose into the nasal cavity. However, in monary delivery, the ability to deliver large qu selectively into the lung, and, more particularly, presents problems. Scintigraphic data obtained suggest that with conventional multidose inha dry powder inhalers most of the drug does not : all²⁰. Some of the dose may be left in the device left in a spacer system (if used), but the majori back of the throat and is then swallowed. For exa cal dry powder inhaler (DPI), one would expe only 10-20% of the dose to reach the lung, an half of this to reach the peripheral region. As a for a peptide molecule one would expect app half of this dose, that reached the alveolar region A simple calculation indicates that for a convent delivery system, the probable achieved bioavaila ence to the original dose, will be relatively smal

Importantly, some of the more recent concept the form of dry powder systems and liquids larger quantities of drug to be delivered into the nificantly, into the deep lung with greater dos. However, bioavailabilities for peptide drugs, even mized dry powder system that provides good dung, will range from 10–20%.

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