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 c
comparison made with pulmona

The nose

The nose has been used for the s
istration of drugs since ancient t
a popular route for the adminis
of abuse such as cocaine, and ir
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 sol
lipophilic in nature (as shown by
ing properties)[1]. The nose is w
and drugs absorbed from the r
pass directly into the blood, v
through the liver, where they wo
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 de
example those with a high first-
as propranolol and steroids, are
sorbed from the nasal cavity with
sophisticated formulations and
hancers. Nicotine provides an ex
that is well absorbed from th
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 tre
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

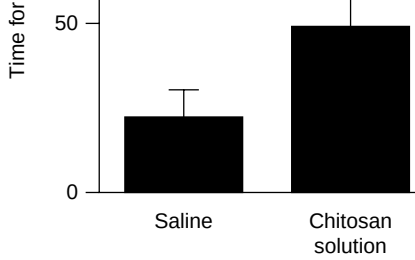
When designing nasal products, it is worth considering some basic physiology. First, when a simple nasal formulation is placed in the nasal cavity (whether as a solution or powder), it will normally be cleared quite rapidly to the throat by a process of mucociliary clearance; the average half-time for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



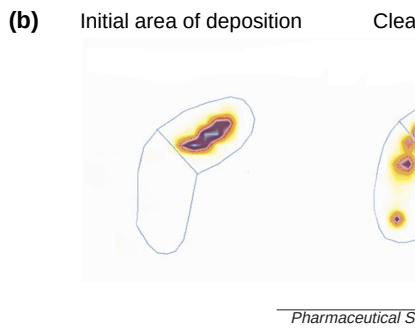


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Figure 1. (a) Clearance of chitosan formulations
of human subjects using gamma scintigraphy; (n
technetium-99m. **(b)** Scintigraphic images showi
formulation in the nasal cavity and clearance to t

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 damag
to screen for such effects in cell cultures, su
animal models[9]. However, some compou
non-damaging but have irritant effects. T
important factor. Nicotine is a good exam
where irritation occurs but the effect is tra
is soon obtained. The measurement of non
can 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 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

chitecture and can be used in a non-anaesthet
also often predictive of results in man; not or
but also quantitatively, especially for peptides
Although the shape of the ovine nose may be
of man, physiological processes, such as mucoc
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 c
dence between sheep and human data[5].

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 imp
approach 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 o
7.0, chitosan is water-soluble and, because of
ture, can bind with mucosal surfaces and with r
occurs through an interaction between the po
amine groups on the chitosan molecule and
charged sialic acid groups on mucin. This inte
bioadhesion and a reduced mucociliary clearan

However, interestingly, chitosan has another
matic effect in terms of providing improved na
tion. Chitosan can alter the paracellular transp
direct effect on the tight junctions between c
shown that the presence of chitosan at a muc
lead to a transient opening of the tight junctio
been demonstrated in CaCO-2 studies, where m
transepithelial resistance, mannitol transport a
measurements have been made[15]. The openi
junctions occurs for a period of approximately
could allow molecules as large as growth hormo
to pass from the nasal lumen into the circula
with molecular weights below approximately

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.

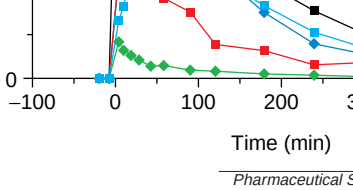

Figure 2. The chitosan effect as measured using a (goserelin) in the sheep model (n = 4). Bioavailab subcutaneous ranges from 1.5% for simple soluti chitosan) to 37% with a chitosan powder system. (black); CHI powder 2 (blue); CHI solution (red); s (green); subcutaneous (light blue). Reproduced, w L.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

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].

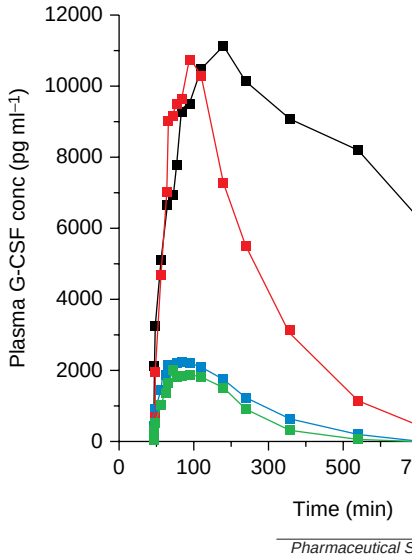

Figure 3. The use of a phospholipid, lysophosphat to enhance the nasal absorption of G-CSF in the s The protein was combined with starch microsphe in solution, and as a mixture of LPG and SMS as a SC 10 μg kg^{-1} (black); SMS 40 μg kg^{-1} (blue); SM (red); LPG 40 μg kg^{-1} (green).

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

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

surfaces; it is the large area that provides for th
tion. Small molecules, such as nicotine, a
species, such as morphine, are apparently rel
sorbed from the central as well as the pe
However, polypeptide molecules, such as insul
absorbed if they are delivered into the deep (al
Data from animal models would suggest tha
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 o

Pulmonary delivery

In the field of nasal delivery, irrespective of whet
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, t
presents problems. Scintigraphic data obtained
suggest that with conventional multidose inha
dry powder inhalers most of the drug does not r
all[20]. Some of the dose may be left in the devic
left in a spacer system (if used), but the majorit
back of the throat and is then swallowed. For exa
cal dry powder inhaler (DPI), one would expec
only 10–20% of the dose to reach the lung, an
half of this to reach the peripheral region. As c
for a peptide molecule one would expect app
half of this dose, that reached the alveolar region
A simple calculation indicates that for a conventi
delivery system, the probable achieved bioavailal
ence to the original dose, will be relatively smal

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

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