REVIEW ARTICLE

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Absorption Enhancers for Nasal Drug Delivery

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Abstract

This paper describes the basic concepts for the transmucosal delivery of drugs, and in particular the use of the nasal route for delivery of challenging drugs such as polar low-molecular-weight drugs and peptides and proteins. Strategies for the exploitation of absorption enhancers for the improvement of nasal delivery are discussed, including consideration of mechanisms of action and the correlation between toxic effect and absorption enhancement. Selected enhancer systems, such as cyclodextrins, phospholipids, bioadhesive powder systems and chitosan,

are discussed in detail. Examples of the use of these enhancers in preclinical and clinical studies are given. Methods for assessing irritancy and damage to the nasal membrane from the use of absorption enhancers are also described. Finally, the mucosal use of absorption enhancers (chitosan) for the improved nasal delivery of vaccines is reported with reference to recent phase I/II clinical studies.

1. Routes of Drug Delivery

Drugs can be delivered by a wide variety of routes, the choice normally depending on factors such as clinical benefit, convenience, cost, the properties of the drug and the pharmacokinetic profile needed. In acute situations, an injectable form may be required, whereas for long-term therapy noninvasive procedures are preferred. Oral administration is usually the modality of choice. However, in some situations, the oral route may not be advantageous. For example, if rapid onset of effect is required, if gastric stasis occurs (e.g. migraine), or if a drug is poorly absorbed across the gastrointestinal tract or is largely degraded by endogenous pH conditions or enzymes within the lumen of the intestine, and/or by first-pass liver metabolism, then oral administration will not be possible.

As a consequence, other noninvasive routes of delivery have been investigated in recent years. These include buccal, nasal and pulmonary routes. The buccal mucosa is normally poorly permeable and absorption can be slow. Delivery to the lungs can provide rapid onset of action but this route is often limited by dose, the irritant nature of certain compounds and effective administration to reach the alveolar region. The nasal route can be the route of choice for a wide range of drugs. This route of delivery will be discussed in more detail below.

2. Nasal Administration of Drugs

The nasal route has the advantage of providing rapid absorption of drugs into the systemic circulation with consequently little or no degradation (no first-pass effect). Many drugs display high bioavailability by this route, particularly if they have lipophilic characteristics, and there is low inter- and intraindividual variability, similar to or lower than for a subcutaneous injection. The route is well received by patients. Disadvantages of nasal administration include problems associated with irritation, taste disturbance and perceived, rather than actual, difficulties with administration and absorption during attacks of colds and rhinitis. A variety of products for the delivery of drugs into the systemic circulation via the nose is available in the market place. These include treatments for pain, smoking cessation and hormone replacement therapy. Products for erectile dysfunction are in development. Nasal administration also has the potential of providing direct access to the brain via the olfactory region. This aspect of nasal delivery has been reviewed by one of us in detail elsewhere.[1]

Lipophilic drugs can be expected to demonstrate rapid and efficient absorption when given nasally, but more polar compounds are poorly absorbed. The products of biotechnology in the form of peptides and proteins are good examples. In animal models and in humans, bioavailabilities of about 1% (versus subcutaneous) are to be expected for compounds such as insulin, calcitonin or leuprolide, and less for higher molecular weight species such as growth hormone, interferons and growth factors. Low-molecular-weight polar compounds such as morphine and sumatriptan, and novel candidates for the treatment of migraine (e.g. alniditan, zolmatriptan), also show poor absorption across the nasal mucosa in the order of 10%. Benefit in terms of improved dose reliability, reduced dose and reduced adverse effects such as taste disturbance could be obtained if it was possible to increase the bioavailability of nasally administered drugs.

The poor uptake of drugs from the nasal cavity can be associated with three major factors:

- poor transport across the nasal membrane (as discussed above);

- possible (enzymatic) degradation in the nasal cavity/tissue;
- rapid clearance from the absorption site.

The second factor is of little consequence for most drugs so far studied to date[2] and will not be discussed further here. However, mucociliary clearance is an interesting problem in nasal drug delivery. In humans, the clearance of mucus from the nasal cavity by the mucociliary clearance mechanism has a half-time of about 15 minutes. Thus, some drugs may not have sufficient time to be absorbed before clearance occurs. Indeed, for some drugs administered nasally, much of the dose is subsequently swallowed and is absorbed from the gastrointestinal tract. Nasal sumatriptan, with a low nasal bioavailability of 16%,[3] is a case in point, where a second peak in the plasma concentration-time profile is probably due to the gastrointestinal absorption of material cleared from the nose. It is likely that two-thirds of the drug reaching the circulation is absorbed from the gastrointestinal tract.

Formulations that are able to slow down the clearance process of drugs from the nasal cavity can therefore be advantageous. However, the critical factor for most challenging drugs is one of absorption across the nasal mucosa and, as a result, considerable effort has been directed towards the development of technologies that can improve the rate and extent of transport of drugs across the membrane. One strategy is to change the physicochemical properties of the drug by making it more lipophilic (e.g. prodrug approach),[4] but this results in a new chemical entity and all the attendant consequences for regulatory approval. Methods to enhance or promote absorption by using formulation additives have therefore been a more popular alternative.

2.1 Peptide Drugs as Candidates for Enhanced Nasal Delivery

Various peptide drugs are currently available as nasal presentations, albeit often with low bioavailability as compared with parenteral (subcutaneous) injection; examples include desmopressin, gonadorelin and its analogues, and calcitonin. Such nasal peptide preparations are described in the Physician's Desk Reference.[5] Nasal sprays of desmopressin are used for primary nocturnal enuresis, haemophilia A, von Willebrand's disease and central cranial diabetes insipidus. No figures for bioavailability are quoted, but a statement is made that desmopressin administered nasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection.[5] Calcitonin nasal spray is used for the treatment of postmenopausal osteoporosis. Interestingly, the mean bioavailability is quoted as approximately 3% of that for the injectable product in normal subjects, with peak plasma concentrations appearing 31–39 minutes after administration (compared with 16–25 minutes after parenteral administration). The quoted range of bioavailabilities is both broad and surprising (0.3–30.6%).[5] The lower value appears reasonable from studies in animals and literature reports on phase I studies and from our own work.[6,7] The higher value of over 30% appears to be extraordinary and can most probably be explained by the limitation in sensitivity of the current bioanalytical methods of analysis. Naferelin nasal spray is used for endometriosis and central precocious puberty; the quoted average bioavailability is 2.8% (range 1.2–5.6%). Nasal products for insulin, growth hormone, interferon and parathyroid hormone are reported to be in development by various pharmaceutical companies.[8]

Hence, low bioavailability can clearly be acceptable for some marketed products, but advantage would be gained in terms of reliability, reduced dose and reduced acquisition costs if nasal absorption could be increased. The same situation holds for polar nonpeptide drugs that are poorly transported across mucosal surfaces.

3. Enhancing the Nasal Absorption of Drugs

A wide range of materials is known to modify the membrane transport of drugs. Some of these are in the form of 'complexing' agents that apparently alter the properties of the drug molecule and thereby aid its passage across the membrane (ion-pair sys-

tems), but the majority have a direct effect on the membrane itself by modifying transport processes.

Drugs can cross biological membranes by two main pathways, transcellular (across the cell) and paracellular (between cells). Lipophilic drugs are normally transported transcellularly by passive diffusion or receptor-mediated processes, whereas polar drugs are believed to follow paracellular pathways. In the gastrointestinal tract, there are transport pathways that facilitate or actively transport certain molecules and attempts have been made to exploit these for drug delivery.[9] Whether such pathways can be used for the nasal cavity is debatable. It is also known that particles can be transported across mucosal surfaces, often via specialised cells called M-cells that are part of the immune surveillance system. Such processes can be important for the development of particulate mucosal vaccines but probably have no relevance for drug delivery.[10] Thus, in order to increase the nasal uptake of polar drugs from the (human) nasal cavity, agents that can alter paracellular transport (and also modify mucociliary clearance) would be beneficial.

3.1 Absorption Enhancers – 'Literature' Perspective

Readers of 'popular' fiction may recall a book by Arthur Hailey entitled *Strong Medicine*[11] that purported to provide an exposé of the pharmaceutical industry. Part of the story concerned the development of a new peptide drug that was to be delivered by nasal spray, with absorption rate improved by inclusion of a detergent. One character described how several detergents had been tested, with "the best non-toxic one, creating no irritation of nasal membranes, … found to be a new product recently available in the United States."

If only it was that easy!

3.2 Absorption Enhancers – Historical Perspective

Table I lists some of the compounds that have been used previously as so-called absorption promoters for the nasal route. Some of these materials have also been evaluated for improving the oral absorption of drugs. Many can be classed as membrane active and have a disruptive effect on both transcellular and paracellular pathways. Although such disruption can be associated with increased drug transport and increased bioavailability, effective compounds are often irritant or can be associated with short- or long-term damage to mucosal tissue. For example, some years ago, bile salts and their derivatives were heralded as safe and effective absorption promoters for peptides and proteins, and even today, surprisingly, one sees clinical investigations using products containing bile salt derivatives. However, it is now appreciated that these promoters are damaging after long-term use. Similarly, fatty acids and surfactants (detergents) such as Laureth-9, while being effective in animal models, cause damage and probably have little utility in clinical practice. Newer surfactant materials, such as the acyl carnitines and acyl maltosides, may be less damaging but could well face regulatory hurdles. The 'trick' is to uncouple a desired improved delivery from an unacceptable level of membrane damage. Even if this goal can be achieved, it will be important to demonstrate that the absorption promoter is not toxic if absorbed systemically.

The older literature on the 'damaging' materials has been well reviewed elsewhere and will not be considered in detail in this article unless there are areas for future investigation or anomalies worth further consideration. For example, in 1994 Verhoef and Merkus[82] considered the relevance of nasal absorption enhancement to nasal drug delivery and listed various materials and their possible modes of action.

Some materials, particularly surfactants, could have more than one effect, e.g. perturbing the cell membrane by leaching of membrane proteins, opening of tight junctions or preventing enzymatic degradation of the drugs. A review by Sayani and Chien,[83] on the systemic delivery of peptides and proteins across absorptive mucosae, contains a useful summary of the different enhancing agents. A listing was included specifically on the nasal delivery of therapeutic peptides arranged by drug (16 in total) and year, beginning 1990 and ending 1993

Table I. Materials used to enhance the nasal absorption of drugs

Enhancer	Drug	Species	Comments	Reference
Surfactants				
Laureth-9	Granulocyte colony stimulating factor	Rat	No effect using sodium glycocholate	12
Laureth-9	Insulin	Man	Type 1 diabetics	13
Laureth-9/sodium deoxycholate	Insulin	Sheep	Surfactants can make interferon aerosols more effective	14
Laureth-9/glycodeoxycholate/ lysophosphatidylcholine	Insulin	Rat	In combination with hydroxypropyl-β-cyclodextrin as protective agent	15
Poloxamer-407/sodium glycocholate/bacitracin	Tetracosactide (ACTH 1–24)	Rat	Bacitracin gave best results	16
Dioctylsulphosuccinate	Polysucrose 1500	Human	Nasal pool device, epithelial damage. Polysucrose as permeation tracer	17
Brij 35 and Brij 96	Insulin	Dog		18
Polysorbate 80	Ciprofloxacin	Rabbit	Bioadhesive systems based on cellulosic materials. Nasal as alternative to oral route	19
Polysorbate 80	Metroprolol	Rat	Decrease in bioavailability	20
Soybean-derived sterol and glucoside mixture	Insulin	Rabbit	Peanut oil formulation	21
Soybean-derived sterylglucoside and β- sitosterol β-D-glucoside	Verapamil	Rabbit	Perturbation of membrane lipid affects paracellular and transcellular pathways	22
Soybean-derived sterylglucoside	Insulin	Rabbit	Powder formulation. No signs of inflammation	23
Alkylglycoside surfactants	Insulin	Rat	Surfactants of different alkyl chain length. Various routes to include nasal	24
Alkylglycosides	Insulin	Rat	Chain length dependence	25
Dodecylmaltoside	Insulin lispro	Rat	Possible effect on tight junctions	26
Quillaja saponin	Insulin	Rat	Low concentration effective	27
Quillaja saponin	Aminoglycosides (gentamicin, tobramycin)	Rat	Various routes. No irritation observed	28
Bile salts and derivatives				
Sodium glycocholate and non-ionic, ionic and amphoteric surfactants	Interferon-β	Rabbit	Solution and powder systems	29
Sodium glycocholate	Insulin	Rat	Various routes compared	30
Sodium glycocholate	Polyethylene glycols	Rat	Structural changes to nasal tissue	31
Sodium glycocholate	Insulin	Human	Type 2 diabetes	32
Sodium glycocholate	Keterolac tromethamine	Rabbit	Bioavailability greater than 80%. Minimal irritation	33
Sodium deoxycholate	Morphine with nanoparticles	Mice	No improvement in antinociceptive effect with enhancer	34
STDHF	Insulin	Rat, rabbit	Interspecies difference	35
STDHF	Insulin	Human	Healthy subjects. 7–9% bioavailability compared with intravenous	36
STDHF	hGH	Rat, rabbit, sheep	Absorption animal-model-dependent	37
STDHF	Insulin	Sheep	Powder formulations	38

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