Absorption enhancing excipients in systemic nasal drug delivery.

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ABSTRACT

Intranasal drug delivery is becoming an increasingly important form of drug administration for chronic and chronic-intermittent diseases. Important new applications currently in development include drugs for diabetes, osteoporosis, obesity, certain types of convulsive disorders, migraine headaches, symptomatic pain relief, nausea, and anxiety, among others. Transmucosal absorption across the nasal mucosa is generally limited to molecules less than 1,000 Da. Systemic delivery of larger molecules requires formulations with a suitable transmucosal absorption enhancer. More than one hundred potential transmucosal absorption enhancing excipients have been tested to date. Nearly all have failed due to poor effectiveness or unacceptable toxicity to the mucosal tissue. Alkylsaccharides, cyclodextrins, and chitosans have emerged as leading candidates for potential broad clinical applications allowing the development of convenient, patient-friendly, needle free formulations of small molecule drugs, as well as, peptide and protein drugs that can be administered at home, at work, or in other public and private settings outside of the doctor’s office or hospital environment.

KEY WORDS: Absorption enhancer, intranasal, drug delivery, chitosan, cyclodextrin, alkylsaccharide

INTRODUCTION

Intranasal drug delivery continues to evolve as an important form of drug delivery. The key aspects driving the growing adoption of nasal delivery include rapid drug absorption compared to subcutaneous injection or oral administration, the avoidance of hepatic first pass effect, greater patient convenience and compliance, and the elimination of needle stick injuries and bio hazardous waste disposal problems associated with the use of syringes. In addition, consumer demographic trends point to an increasing popularity of self-administration of drugs for personal management and the control of chronic diseases. Topical nasal applications such as therapies for nasal congestion and allergic rhinitis still account for the major share of
intranasal drug delivery. However, nasal administration of drugs intended for systemic absorption in the treatment of chronic diseases such as diabetes, osteoporosis, obesity, certain types of convulsive disorders, migraine headaches, together with symptomatic relief of pain, nausea, and anxiety is rapidly growing. The US market alone for intranasal drug delivery is projected to reach US $4.4 billion by the year 2015.

**ADVANTAGES OF INTRANASAL DELIVERY AND SOME EXAMPLES**

Nasal delivery is suitable for the treatment of chronic conditions such as diabetes, osteoporosis, obesity, as well as, chronic-intermittent conditions such as migraine or breakthrough seizures. In general, intranasal delivery provides a convenient, patient-friendly, nonthreatening, needle free, pain free, administration route allowing for self-administration at home, at work, or in other public settings. As an example of improved convenience, at present the only approved out-of-hospital treatment for breakthrough seizures, in the US, is a diazepam rectal gel (Diastat®). Because of its inconvenient administration route it is prescribed essentially only for infants or very young children. Affected adults must wait for emergency treatment to arrive, transportation to hospital, intravenous administration of diazepam together with an overnight observational stay at a total cost of approximately US $3,000, or more. A novel formulation, developed by San Diego-based Neurelis Corporation, incorporating a highly effective absorption enhancer has allowed the otherwise poorly nasally absorbed diazepam to be delivered with 96% absolute systemic bioavailability (1). As a replacement for rectal gel, it allows immediate treatment on-site and provides an excellent illustration of the importance of nasal delivery as a convenient alternate delivery mode.

An example of the benefit of increased speed of systemic absorption that can be achieve through nasal delivery is shown in Figure 1. Figure 1 shows a comparison of the pharmacokinetics of nasal administration of sumatriptan containing the specific absorption enhancer dodecyl maltoside (DDM) with nasal administration of the same dose of sumatriptan in the absence of DDM. The $T_{\text{max}}$ of nasally administered sumatriptan in the presence of the absorption enhancer is approximately 8 minutes compared to approximately 60-120 minutes for the currently available nasally administered sumatriptan. The DDM-enhanced nasal formulation reaches an equivalent therapeutic blood level in only 2-3 minutes, approximately 20-30 times faster than currently commercially available oral or nasal products (2).

Intranasal delivery can the speed absorption of much larger, otherwise injectable-only peptide drugs, as well. For peptides or proteins such as insulin, leptin, or growth hormone the $T_{\text{max}}$ values for nasal administration have been shown to be one half or less of the corresponding $T_{\text{max}}$ values for injections of these same proteins (3, 4).

Avoiding the hepatic first-pass metabolism effect is another advantage of systemic nasal delivery. Bypassing the GI tract allows more reliable and reproducible bioavailability to be achieved. Drugs that undergo extensive first-pass metabolism, display erratic absorption, or require quick therapeutic onset are potentially good drug candidates for intranasal delivery, particularly those that would otherwise require an injection.

**NASAL ANATOMY, PHYSIOLOGY, AND ABSORPTION PROCESSES**

The nose is divided into two nasal cavities by the septum, each with a volume of approximately 7.5 ml and a surface area of approximately 75 cm$^2$ (5, 6). Of the three distinct functional regions in the nose, namely, the vestibular, respiratory, and olfactory regions, the respiratory region is the largest and comprises approximately 65 cm$^2$. It is highly vascularized and is the principal site of systemic drug absorption (6). The respiratory epithelium
Figure 1 The absorption enhancement effect of DDM on the plasma profile of nasally administered sumatriptan in humans (mean ± S.D.). T<sub>max</sub> is reduced from 60-120 for the currently marketed nasal or oral sumatriptan down to 8 minutes with equivalent therapeutic levels achieved at 2 minutes, and the bioavailability as measured by the AUC (area under the curve) is significantly increased.

consists of basal cells, mucus-containing goblet cells, ciliated columnar cells, and non-ciliated columnar cells (5, 6). The cilia are surrounded by a film of mucus and move in a continuous wavelike fashion to transport mucus and entrapped particles to the pharynx for ingestion (6 - 8).

Mucus is a viscous colloid comprised of mucins (glycoproteins that are produced by goblet cells in the mucous membranes and submucosal glands), together with antibacterial proteins such as lysozyme and lactoferrin, immunoglobulins, and inorganic salts (9). The constantly regenerating mucus coating moves at 5 to 6 mm/min. (5, 10) and serves to protect epithelial cells from external insults (viruses, bacteria, and chemical irritants). By restricting drop size in nasally administered sprays to a diameter >10 µm deposition is restricted to the nasal cavity and lung exposure is essentially zero (11-14). The pH range of the nasal cavity is approximately 5.5 to 6.5 so nasal irritation is minimized when products are formulated within this pH range (15, 16). The total spray volume that can be reliably delivered to each naris is limited by the size of the nasal cavity and generally thought to be no more than 150 µl and the upper limit of a drug dose has been suggested to be 25 mg/dose (16).

**ABSORPTION ENHANCING EXCIPIENTS**

There are two primary mechanisms for absorption through the mucosa. They are paracellular transport via opening of tight junctions between cells, and transcellular transport or transcytosis through cells via vesicle carriers (3, 17). Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and, limited residence time in the cavity. Some transmucosal absorption enhancers function by altering either or both the paracellular and transcellular
pathways, while others serve to extend residence time in the nasal cavity or prevent metabolic changes, e.g., unwanted peptide hydrolysis.

Dozens of excipients have been tested as potential enhancers of intranasal absorption over the course of the last three decades in the hope that alternate noninvasive means of administering peptides, proteins, and small molecule drugs might be achieved. Table 1 lists some of these. Nearly all of the molecules tested to date have been shown to cause significant and, in some cases, serious damage to the nasal mucosa upon repeated administration, especially at concentrations high enough to achieve a substantial degree of transmucosal absorption enhancement. Indeed, the principal factors limiting broad acceptance of intranasal administration have been damage to the nasal mucosa coupled with poor transmucosal absorption caused by the absorption enhancers. The few exceptions, which include the alkylsaccharides, cyclodextrins, and chitosans, are among the most effective and are generally well tolerated, with varying degrees of effectiveness as absorption enhancers.

In the absence of an absorption enhancer, the apparent molecular weight cut-off point for nasal absorption is approximately 1,000 Da, with molecules less than 1,000 Da having better absorption (43). Co-administration of drugs with absorption enhancers promotes the absorption of drugs ranging in size from 1,000 Da to 31,000 Da. The principle mechanisms for increased absorption are loosening of tight junctions between cells, enhanced vesicular transcytotic transport, alteration of the rheological (fluidity) properties of the mucus and/or alteration of the cilia (i.e., paralysis of ciliary beating or removal of cilia from the epithelial cells that line the nasal cavity (3, 23, 44-52). The latter two mechanisms serve to increase the residence time of drug in the nasal cavity allowing more time for passive diffusion.

**Table 1** Some examples of molecules that have been used as transmucosal absorption enhancers. Excipients used in human trials are shown in bold. Of these, excipients exhibiting no reported irritation are marked with an asterisk (*).

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Reference(s)</th>
</tr>
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<tbody>
<tr>
<td>Aprotinin (18)</td>
<td></td>
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<tr>
<td>Benzalkonium chloride* (19)</td>
<td></td>
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<tr>
<td>Benzyl Alcohol (20)</td>
<td></td>
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<tr>
<td>Capric acid, sodium salt (21)</td>
<td></td>
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<tr>
<td>Ceramides (22)</td>
<td></td>
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<tr>
<td>Cetylpyridinium chloride (19)</td>
<td></td>
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<tr>
<td>Chitosan* (23)</td>
<td></td>
</tr>
<tr>
<td>Cyclodextrins* (22)</td>
<td></td>
</tr>
<tr>
<td>Deoxycholic acid (24)</td>
<td></td>
</tr>
<tr>
<td>Decanoyl carnitine (21)</td>
<td></td>
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<tr>
<td>Dodecyl maltoside* (4)</td>
<td></td>
</tr>
<tr>
<td>EDTA (21)</td>
<td></td>
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<tr>
<td>Glycocholic acid, sodium salt (25)</td>
<td></td>
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<tr>
<td>Glycodeoxycholic acid, sodium salt (25)</td>
<td></td>
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<tr>
<td>Glycofurol (26)</td>
<td></td>
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<tr>
<td>Glycosylated sphingosines (22)</td>
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<tr>
<td>Glycyrrhetinic acids (27)</td>
<td></td>
</tr>
<tr>
<td>2-Hydroxypropyl-β-cyclodextrin (28)</td>
<td></td>
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<tr>
<td>Laureth-9 (29)</td>
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<tr>
<td>Lauric acid (30)</td>
<td></td>
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<tr>
<td>Lauroyl carnitine (31)</td>
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<td>Lauryl sulfate, sodium salt (25)</td>
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<td>Lysophosphatidylcholine (29)</td>
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<tr>
<td>Menthol (32)</td>
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<tr>
<td>Poloxamer 407 (33)</td>
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<td>Poloxamer F68 (34)</td>
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<tr>
<td>Poly-L-arginine (35)</td>
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<tr>
<td>Polyoxyethylene-9-lauryl ether (25)</td>
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<tr>
<td>Polysorbate 80 (34)</td>
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<tr>
<td>Propylene glycol (36)</td>
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<tr>
<td>Quillaja saponin (37)</td>
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<td>Salicylic acid, sodium salt (20)</td>
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<tr>
<td>β-Sitosterol-β-D-glucoside (38)</td>
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<tr>
<td>Sucrose cocoate (39)</td>
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<tr>
<td>Taurocholic acid, sodium salt (40)</td>
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<tr>
<td>Taurodeoxycholic acid, sodium salt (41)</td>
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</tr>
<tr>
<td>Taurodihydrofusidic acid, sodium salt (42)</td>
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<tr>
<td>Tetradecyl maltoside (2)</td>
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**TOXICITY ASSESSMENT**

Two principal requirements for useful absorption enhancers are significant effectiveness and safety. Extensive in vivo studies aimed at assessing the effectiveness and
toxicity of more than 50 possible absorption enhancers were conducted by Chen et al. (22) using the measurement of transepithelial electrical resistance across confluent cell layers comprised of cultured human bronchial/tracheal epithelial cells in a microtiter well format. If exposure to the cells by one of the 50, or so, test excipients resulted in a reduction in transepithelial electrical resistance (TEER) across the confluent cell layer, it was interpreted as an opening of tight junctions between the cells. Similar studies have been repeated by Vllasaliu et al. using Calu-3 cells (53). The reduction in TEER in vitro seems to correlate with potential absorption enhancement properties in vivo though the correlation is not by any means perfect.

Attempts to use this same cell based model for toxicity assessment is not predictive because of gross difference between the in vitro and in situ cell environments. In vitro cell culture models of nasal mucosa are understandably deficient from a number of perspectives. Some of these deficiencies apply in general to assessment of all excipients and some are deficiencies specific to the particular excipient being tested. From a general deficiency perspective, both studies exposed the naked confluent cells in culture media to excipients for 60 to 120 minutes at 37°C. During this time, the naked cells were continuously exposed to continuous high concentrations of the excipient.

In contrast, in the nasal cavity, the epithelial cells lining the nasal cavity are bathed in a constantly regenerating mucus coating that flows at a rate of 5 - 6 mm/min. resulting in a mucociliary clearance time of approximately 15 minutes. Thus the contact time of exposure of nasal epithelia, and the concentration of both excipient and drug is progressively and continuously reduced by three means i.e., dilution into the mucus, absorption into the systemic circulation, and physical removal through the mucociliary clearance mechanism. Assuming a linear concentration reduction over 15 minutes the integrated exposure (i.e., time X concentration) to excipient is lower by a factor of 8- to 16-fold in the physiological circumstance compared to the 60 to 120-minute incubation times, respectively, for the naked cells. Further, the intrinsic properties of mucus whose complex composition of mucin glycoproteins, lysozyme, lactoferrin, and immunoglobulins, is precisely designed as a natural protection against external insults cannot be factored into the in vitro cell assay.

ALKYLSSACCHARIDES

Alkylglycosides and sucrose esters of fatty acids are nonionic alkylsaccharide surfactants that consist of an aliphatic hydrocarbon chain coupled to a sugar moiety by a glycosidic or ester bond, respectively. The particular alkylsaccharides that were shown to be effective absorption enhancers are odorless, tasteless, non-toxic, non-irritating, non-mutagenic, and non-sensitizing in the Draize test at concentrations of up to 25% (54, 55). They are synthesized as single chemical entities composed of a sugar, typically a disaccharide, and an alkyl chain, typically 10 to 16 carbon atoms in length. They provide controlled transient permeation of the nasal mucosal barrier with no irritation. Following absorption or ingestion they metabolize to CO₂ and H₂O through the corresponding sugar and fatty acid (56, 57).

Alkylglycosides are widely used in the food industry. For example, they are sprayed on fruits and vegetables to prevent the growth of bacteria and fungi or, used to clean food processing equipment, primarily because of their intrinsic and highly effective antimicrobial activity and lack of toxicity. The EPA has determined that there is no need to establish an upper limit of exposure for adults, children or infants (58).

Similarly, sucrose esters find widespread use as food-grade emulsifiers and in cosmetic preparations. The No Observed Effect Level (NOEL) for these molecules is as high as 2,000 mg/kg body weight in some instances (56) and are designated as Generally Recognized As Safe (GRAS) substances for food applications. They
are used in such small amounts that the WHO oral allowable daily intake (ADI) is nearly 10,000 times (56) the amount that would be used in a typical single nasal spray dose (i.e., 200 µg/spray versus 2 g/day ADI).

Despite the accumulation of considerable experimental evidence concerning the efficacy of alkylglycosides as absorption-enhancers, their mechanism of action remains unknown. Alkyl maltosides appear to enhance transmucosal delivery of peptides through transcellular, and paracellular, pathways (3, 59). Transmission electron micrographs of the nasal septa of rats show, immediately after the exposure to alkyl maltoside, unstained regions that are consistent with cellular internalizations and areas of thinned cilia associated with vesicle formation (3). The transcellular pathway is further supported by fluorescence light micrographs showing the internalization of fluorescein-labeled insulin administered intranasally with an alkyl maltoside (3). As stated above, the paracellular pathway is nominally demonstrated by a decrease in the transepithelial electrical resistance (TEER) and an increase in mannitol movement across a confluent layer of human bronchial epithelial cells in the presence of tetradecyl maltoside (36).

Studies have shown that alkylglycosides and sucrose esters are among the most effective nasal absorption enhancers for a wide range of peptide, protein, and non-peptide macromolecular drugs in rats, mice, cats, dogs and monkeys (60-66). Dose-escalation studies were conducted in rats to determine the potencies of various alkylglycosides and sucrose esters in increasing nasal absorption of insulin and to determine the contribution of the alkylchain and the sugar moiety. These studies revealed that shorter chained alkylsaccharides coupled to glucose, such as hexyl, heptyl, octyl or nonyl glucoses, were ineffective, or minimally effective, at promoting insulin absorption from the nose (63, 65). Intermediate-length alkylsaccharides such as decanoyl sucrose, decyl maltoside, or octyl maltoside were more effective in promoting nasal insulin absorption. Longer chain alkylsaccharides such as dodecyl maltoside, tridecyl maltoside, tetradecyl maltoside, and sucrose dodecanoate were very potent absorption enhancers, even at concentrations as low as 0.03-0.06%. No other absorption-enhancing agents tested to date have been as effective at such low concentrations. Interestingly, increasing the alkyl chain length beyond 14 carbons (e.g., pentadecyl maltoside, or hexadecyl maltoside) decreases the potency of nasal insulin absorption.

**CYCLODEXTRINS**

Cyclodextrins (CD) are cyclic oligosaccharides composed of six or more monosaccharide units with a central cavity. Cyclodextrins can form inclusion complexes with hydrophobic molecules and they have primarily been used to increase drug solubility and dissolution and to enhance low molecular weight drug absorption (67, 68). Among the cyclodextrin derivatives studied as potential nasal insulin absorption enhancers, dimethyl-beta-cyclodextrin was found to be the most effective, while alpha-CD was less effective and beta- and gamma-CD had negligible effects on insulin absorption (69). Cyclodextrins are believed to interact with cholesterol within the cell membrane (70). This interaction transiently opens tight junctions which may explain their ability to facilitate peptide absorption across the nasal mucosa (49). Since not all cyclodextrins are effective at increasing peptide bioavailability, the architecture of the central cavity appears to be critical for nasal peptide drug absorption. Previous work has demonstrated that dimethyl-beta-cyclodextrin was effective in promoting the absorption of a number of drugs including insulin (72, 73), calcitonin (40), and low molecular weight heparin (74). Gamma cyclodextrin is ineffective at increasing peptide drug absorption.
CHITOSAN

Chitosan is a linear cationic polysaccharide produced from the deacetylation of chitin, a component of the shells of shrimp and other crustaceans (7, 79, 80). Chitin is composed of randomly distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine joined by glycosidic bonds.

Chitosan has been shown to increase the bioavailability of insulin and other small peptides and polar macromolecules in different animal models (75-77). Chitosan exhibits bioadhesive properties and interacts strongly with nasal mucus layer enhancing the contact time for drug with membrane. The addition of 0.2-0.5% chitosan to nasal formulations of insulin resulted in significant increases in plasma insulin and reductions in blood glucose in both sheep and rat models. Studies in human volunteers demonstrated that nasal administration of chitosan formulations results in significantly longer nasal clearance times (78) suggesting that chitosan decreases mucociliary clearance and prolongs the residence time of peptides within the nasal cavity (79-86). Chitosan also produces a transient opening of tight junctions of confluent Caco-2 cells (87).

BILE SALTS AND DERIVATIVES

Attempts to administer insulin non-invasively through the nasal route using bile salts date back nearly three decades (42) with mixed results. Bile salts and their derivatives, such as sodium glycocholate, sodium taurocholate, and sodium taurodihydrofusidate, were shown to effectively promote nasal insulin absorption (41, 45, 88, 89) and were subsequently extensively studied for their ability to promote the absorption of a variety of peptide drugs from several alternative delivery sites (90, 91). The mechanisms of action by which the bile salts/derivatives promote increased nasal absorption of peptide drugs are not well understood. Possible explanations may include the fluidization of the nasal epithelial cell membranes, increases in transcytotic movement of peptides via endocytic vesicles, or the inhibition of certain proteolytic enzymes capable of degrading peptides before they can successfully cross the nasal epithelium. Inclusion of sodium glycholate in an insulin formulation resulted in a significant reduction in enzymatic degradation of insulin (92). Through circular dichroism and alpha-chymotryptic degradation studies, a dose-response relationship between increasing concentrations of sodium glycholate and the presence of monomeric insulin has been shown (92). Similarly, sodium taurocholate has been shown to increase disaggregation of insulin hexamers in a dose dependent manner (92). Unfortunately, in test subjects bile salts and derivatives were found to produce significant nasal irritation, stinging and lacrimation. So while early attempts to administer insulin using bile salt-based formulations successfully achieved useful systemic blood levels and a corresponding reduction in blood glucose levels, the resulting nasal damage was unacceptable and not tolerated by test subjects. This experience with the bile salt excipients illustrates the most significant challenge for the practical broad adoption of nasal drug delivery.

COMPARATIVE STUDIES

The three types of absorption enhancers that have been studied most extensively, namely alkylsaccharides, cyclodextrins, and chitosan, have proven useful for nasal delivery of small molecule drugs, as well as, for peptide and protein drugs. Each offers potential advantages over the others in specific applications. For example, chitosan has proven useful as an absorption enhancer for both aqueous solution and dry powder formats. Cyclodextrins have been used in aqueous solutions where they not only increase transmucosal absorption, but can also increase solubility of hydrophobic drugs. Alkylsaccharides, which provide the greatest degree of absorption enhancement in most applications, are soluble in aqueous and oil-based/organic liquid formulations and are being used in both formats. In addition, alkylsaccharides prevent peptide and protein
Table 2: Comparison of the absolute bioavailability for intranasally administered calcitonin using three different absorption enhancers.

<table>
<thead>
<tr>
<th>TEST ARTICLE</th>
<th>EXCIPIENT</th>
<th>ABSOLUTE BIOAVAILABILITY</th>
<th>TOTAL DOSE ADMINISTERED</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous calcitonin control</td>
<td>none</td>
<td>100%</td>
<td>10 IU/KG</td>
<td></td>
</tr>
<tr>
<td>Nasal calcitonin, in pH 4 isotonic phosphate buffer</td>
<td>1% chitosan free amine</td>
<td>2.45%</td>
<td>10 IU/KG</td>
<td></td>
</tr>
<tr>
<td>Nasal calcitonin, in pH 4 isotonic phosphate buffer control</td>
<td>5% dimethyl-beta-cyclodextrin</td>
<td>1.91%</td>
<td>10 IU/KG</td>
<td>(28)</td>
</tr>
<tr>
<td>Nasal calcitonin in pH 4 isotonic phosphate buffer</td>
<td>None</td>
<td>1.22%</td>
<td>10 IU/KG</td>
<td></td>
</tr>
<tr>
<td>Nasal calcitonin in pH 3.75, 6 mM sodium acetate, 0.9% sodium chloride</td>
<td>0.125% tetradecyl maltoside</td>
<td>52%</td>
<td>8 IU/KG</td>
<td>(66)</td>
</tr>
</tbody>
</table>

aggregation (93, 94). There are few direct comparative studies assessing differences in absorption enhancement efficiency in the literature. Published studies on the nasal bioavailability of calcitonin, a peptide drug 32 amino acids in length with an approximate molecular weight of 3,500 Da (66, 93) provides one such example. Sinswat et al. (28) compared the absolute bioavailability of calcitonin administered nasally to rats using cyclodextrins and chitosan’s as the absorption enhancers to intravenous calcitonin as the control. Ahsan et al. carried out a similar study, again in rats, using alkylsaccharide tetradecylmaltoside as the absorption enhancer, again using intravenous administration as the control (66). The results are shown above in Table 2.

In these side by side comparisons, the formulation containing the alkylsaccharide excipient tetradecyl maltoside was found to be significantly more effective than either of the formulations containing chitosan or dimethyl beta cyclodextrin.

Data from a study comparing intranasal absorption of a GLP-1 analog oligopeptide in Sprague Dawley rats are shown in Figure 2. In this study, two alkylsaccharides, dodecyl maltoside (DDM) and sucrose dodecanoate (SDD) were compared to the bile acid absorption enhancer sodium taurocholate, together with Tween 20 (polysorbate-20) and phosphate buffered saline as a negative control. Rats were anesthetized using isoflurane/O_2 mixture and dosed with 40 µg of the GLP-1 analog by instillation of a 20 µl drop into a single naris. Solutions of the GLP-1 analog and excipient (DDM, SDD, sodium taurocholate, Tween-20) were prepared in 20 mM phosphate buffer, pH 7.0. Each group of 12 rats was matched by body weight. Blood samples were drawn at the timed intervals shown and assayed.

The molecular weight of GLP-1 at 4,112 Da is slightly larger than calcitonin, but very much within the molecular weight range suitable for intranasal peptide administration. Of the two alkylsaccharides tested, dodecyl maltoside appeared to be better than sucrose dodecanoate and both were superior to sodium taurocholate. The polysorbate surfactant Tween-20 exhibited no absorption enhancement and was comparable to the phosphate buffer control.
CONCLUSION

More than one hundred potential transmucosal absorption enhancing excipients have been tested to date. Nearly all failed due to poor effectiveness or unacceptable toxicity to mucosal tissue. Alkylsaccharides, cyclodextrins, and chitosan’s have emerged as the leading candidates for potential broad clinical applications. Certain molecules from all three types are able to exert their desired effects without causing transmucosal damage and all three have demonstrated clinical utility in human studies together with demonstrated safety and lack of intranasal toxicity. A principal mechanistic benefit shared by these absorption enhancing excipients is the fact that they function independently of the drug, that is, they act on the transmucosal membranes and do not require a modification of the drug substance. It is certainly desirable that additional research is carried out to identify better alternatives. In undertaking such research there are two impediments that must be overcome. First, there is a practical limit to the size of molecules that can be absorbed transmucosally. A practical molecular weight limit is estimated to be in the range of approximately 25 – 30 kDa. This is because there is a physical limit to the extent to which tight junctions can be opened without tissue damage. Absorption by the transcellular route is not subject to similar size limitation and may even allow absorption of nanoparticles, well beyond the size of soluble peptide or protein molecules (95). It is possible that a combination of excipients which separately maximize paracellular and transcellular absorption could be worth pursuing. Nevertheless, it may be difficult to develop alternative excipients that exceed the performance of those tested to date without causing unacceptable tissue damage. A second impediment and practical “real world” concern relates to the regulatory requirement to assess the potential for toxicity before being permitted to conduct human clinical trials. In every case, care must be taken to fully assess the potential for toxicity upon chronic administration of novel excipients.

Today, literally thousands of patients have been exposed to intranasal administration of drugs using alkylsaccharides, cyclodextrins, and chitosan’s and thus there is a growing database of safety experience with these excipients. Because of the ever-increasing cost of preclinical, as well as, clinical studies the cost to duplicate this experience base in itself has become somewhat of a significant impediment.

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