Guest Editorial

Mucoadhesion; A prerequisite or a constraint in nasal drug delivery?

Nasal drug administration has frequently been proposed as the most feasible alternative to parenteral injections. This is due to the high permeability of the nasal epithelium, allowing a higher molecular mass cut-off at approximately 1000 Da and the rapid drug absorption rate with plasma drug profiles sometimes almost identical to those from intravenous injections. Nasal drug administration is presently used for local therapies within the nasal cavity. Anti-allergic drugs and nasal decongestants are the most common examples. However, nasal drug administration for systemic effects has been practiced since ancient times. Nasally-administered psychotropic drugs by native Indians, the use of tobacco snuffs, and nasal administration of illicit drugs such as cocaine are all well known.

The use of the nasal cavity as a route for drug delivery has been an area of great interest to the pharmaceutical industry during the last few decades. This area is characterized by a high degree of maturity; a few novel chemical entities have been developed, and the focus is on improvisation of the formulations. There has also been a great interest in developing products for systemic delivery of drugs such as small molecular drugs (e.g. sumatriptan), peptides (e.g. desmopressin) and proteins (e.g. insulin) that are not easily administered via routes other than injection or where a rapid onset of action is required. The use of the nasal cavity for vaccination has also been an area of interest. Nasal drug delivery has now been recognized as a very promising route for delivery of therapeutic compounds including biopharmaceuticals.

Nasal drug delivery offers many attractive possibilities, such as systemic delivery of drugs with avoidance of first-pass metabolism, easy administration, rapid onset of effect and the possibility to circumvent the blood-brain barrier. It also offers both systemic and local vaccine response and of course avoidance of adverse systemic effects when treating local nasal ailments. Not surprisingly, nasal administration has therefore attracted great interest from both the industry and academia. The widespread interest in the intranasal route for therapeutic purposes other than the topically administered nasal drug delivery arises from the particular anatomical, physiological and histological characteristics of the nasal cavity, which provides potential for rapid systemic drug absorption and quick onset of action. In addition, intranasal absorption avoids the gastrointestinal and hepatic presystemic metabolism, enhancing drug bioavailability in comparison with that obtained after gastrointestinal absorption. On the other hand, intranasal administration also offers several practical advantages either from the viewpoint of patients (non-invasiveness, essentially painless, ease drug delivery and favourable tolerability profile) or pharmaceutical industry (unnecessary sterilization of nasal preparations). Hence, bearing in mind the intrinsic value of the intranasal route to overcome patient compliance concerns together with its pharmacokinetic advantages, it appears to be an appropriate route for the treatment of not only acute or chronic nasal diseases, but also for a range of acute or chronic conditions requiring considerable systemic drug exposure. Despite the potential of nasal drug delivery, it has a number of limitations.

One problem with nasal administration is the rapid removal of mucus from the nasal cavity, resulting in a clearance half-life of about 15 min for ordinary formulations. Mucoadhesion, allowing prolonged retention time, is therefore often considered a prerequisite for effective nasal administration. Over the last few decades, the application of mucoadhesive polymers in nasal drug delivery systems has gained interest among pharmaceutical scientists as a means of promoting dosage form residence time in the nasal cavity as well as improving intimacy of contact with the absorptive membranes of the biological system. In addition, the enhanced paracellular absorption following the swelling of the mucoadhesive polymers on the nasal membranes provides an important way for the absorption of the macromolecules through the nasal cavity. It has been demonstrated that low absorption of drugs can be countered by using absorption enhancers or increasing the drug residence time in the nasal cavity, and that some mucoadhesive polymers can serve both functions.

Mucoadhesion is where two surfaces, one of which is a mucous membrane, adhere to each other. This has been of interest in the pharmaceutical sciences in order to enhance localized drug delivery, or to deliver 'difficult' molecules (proteins and oligonucleotides) into the systemic circulation. Mucoadhesive materials are hydrophilic macromolecules containing numerous hydrogen bond-forming groups, the carbomers and chitosans being two well-known examples. The mechanism by which mucoadhesion takes place has been said to have two stages, the contact (wetting) stage followed by the consolidation stage (the establishment of the adhesive interactions). The relative importance of each stage will depend on the individual application. For example, adsorption is a key stage if the dosage form cannot be applied directly to the mucosa of interest, while consolidation is important if the formulation is exposed to significant dislodging stresses. Adhesive joint failure will inevitably occur as a result of over-hydration of a dosage form, or as a result of epithelia or mucus turnover. New mucoadhesive materials with optimal adhesive properties are now being developed, and these should enhance the potential applications of this technology. The mucoadhesive polymers have enormous potential for the delivery of therapeutic macromolecules, genes, and vaccines through the nasal cavity with high drug bioavailability.

The most common way to achieve mucoadhesion is by addition of polymers to the formulation. These polymer-based mucoadhesive drug delivery systems can be divided into three general groups: (I) polymers that adhere due to stickiness, (II) polymers that adhere mostly through electrostatic interactions, and (III) polymers that bind through specific receptor sites. The first two categories are nonspecific, and can potentially adhere to any suitable surface, while the third category of polymers are intended for targeted mucoadhesion. An alternative route to mucoadhesion may be to use liquid crystalline phases, where a low-viscosity phase is administered, and subsequently the phase changes into a more highly viscous phase with longer retention time.

Mucoadhesive agents are hydrocolloids that form weak covalent, hydrogen and ionic bonds with the mucus and thereby decrease mucociliary clearance. The presence of a mucoadhesive agent can alter the viscosity, rheology and the ciliary beating frequency (CBF). The CBF depends on the presence of calcium in the nasal environment. The mucoadhesive agents that can form complexes with calcium (like polyacrylic acid) decrease the CBF thus prolonging residence time. However, this mechanism of mucoadhesives can raise safety concerns that need to be assessed as an important pharmaceutical consideration. Any alteration in mucociliary clearance will interfere with the clearance of nasal contaminants into the gastrointestinal tract, allowing opportunistic microorganisms to grow and cause upper respiratory tract infections.

In general, addition of polymers and especially those belonging to Group I that rely on water absorption, will lower the water activity and impose a larger gradient in water activity over the mucosa. This means that in addition to prolonging retention time, the formulation may also induce a mucosal response, as dehydration can affect the structure and barrier properties in contra-productive ways. The intriguing question is whether a topically applied formulation with low water activity, that favors mucoadhesion, would also induce a mucosal response detrimental to drug absorption.

The term 'water activity' describes the equilibrium amount of water available for hydration of materials. When water interacts with solutes and surfaces, it is unavailable for other hydration interactions. A water activity value of unity indicates pure water whereas zero indicates the total absence of 'free' water molecules; addition of solutes always lowers the water activity. Water activity reflects a combination of water-solute and water-surface interactions plus capillary forces. The nature of a hydrocolloid or protein polymer network can thus affect the water activity, cross-linking reducing the activity. Control of water activity (rather than water content) is very important as low water activity causes large changes in textural characteristics. The activity coefficient is an equilibrium property and most materials during preparation and/or processing will not be at equilibrium and so their properties may diverge from those expected from their activity coefficients.

Mucoadhesion is often achieved by water sorption into the product, while research on skin barrier response has shown a general decrease in drug permeability on increasing the gradient in water activity. A similar effect has been seen in preliminary results on oral mucosa and it is thereby not farfetched to expect the same behavior from nasal mucosa. If so, this would be a general effect relevant to any formulation applied topically, that should be measured or calculated in advance to anticipate the potential detrimental effects on mucosal absorption prior to *in vivo* tests, and therefore highly relevant in formulation development. Nasal mucoadhesives have been extensively investigated for the delivery of small organic molecules, antibiotics, proteins, vaccines and DNA and with many new classes of functionalized mucoadhesive polymers round the corner, the characterization and safety aspects of nasal drug products should be ensured.

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