Transnasal Drug Delivery – An Expanding Technology

a report by

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The potential for transnasal delivery of drugs has been recognised for many years and is currently an area of accelerating interest and development by the pharmaceutical industry both in the US and abroad. While there are specific challenges to effective drug delivery with this method – as is the case with all routes of drug delivery – the advantages of transnasal drug delivery will make it one of the fastest growing methods over the next five years.

Advantages of Transnasal Drug Delivery

One distinct advantage of transnasal drug delivery is that drug uptake into the blood circulatory system by absorption through the nasal mucosa can be quite rapid.[1,2] An aerosol containing a biologically active agent can produce its effect very rapidly.[3] Transnasal drug delivery may be the delivery route of choice for drugs for brain disorders such as migraine headaches, since there may be direct access from the nasal cavity to the central nervous system (CNS) via the olfactory neurons, thus avoiding the problems with the blood–brain barrier observed for drugs administered intravenously; however, this remains to be confirmed and quantified.

Another distinct advantage of transnasal drug delivery over conventional oral drug administration in the form of drug-containing tablets and liquids is the avoidance of low pH, associated chemical degradation, enzymatic inactivation and hepatic extraction. Because of the harsh environment of the stomach, excipients may need to be included during tablet formulation to ensure drug survival and to maximise the uptake of drugs into the blood circulatory system. In addition, certain drugs – such as aspirin – are often enterically coated to avoid adverse effects in the stomach until their subsequent dissolution and uptake in the small intestine. Indeed, intestinal proteases can attack protein/peptide drugs, making transnasal delivery of such drugs a potentially interesting alternative. However, it should be remembered that as oral drug delivery developed historically as the major – indeed, almost exclusive – route of drug administration, an enormous body of science has evolved and continues to grow that focuses on maximising the survival of drugs administrated orally and their efficient and effective uptake by the blood circulatory system.

Vastly different and much less stringent considerations must be given to drug uptake into the blood circulatory system via transnasal drug administration.[3,4] Since the predominant mechanism employed for transnasal delivery is typically use of an aerosol containing the drug, consideration must be given to the plume geometry – and, to some extent, the kinetics of release – of the aerosol to ensure the highest possible deposition and retention of the drug-containing aerosol particles by the nasal mucosa. Particle sizes too large will have less nasal penetration, while particle sizes too small can bypass the nasal mucosa and reach the throat oral cavity and be swallowed into the stomach or inhaled into the lungs.

In addition, one must distinguish clearly between device designs for transnasal drug delivery of an aerosol-containing drug that focus on maximising nasal mucosal uptake of the drug into the blood circulatory system, and device designs that focus on maximising oral inhalation delivery of an aerosol-containing drug to the respiratory tract and the lungs. A common type of device for oral inhalation drug delivery is the metered dose inhaler (MDI), which is inserted into the mouth instead of the nose. MDI and transnasal administration have been under serious consideration for US Food and Drug Administration (FDA) approval and are being clinically evaluated by Eli Lilly and a number of other companies for delivery of insulin in aerosol form to the lungs for blood circulation uptake. This offers the potential benefit of ultimately replacing the historic administration of insulin to insulin-dependent diabetics by insulin injections. Some concerns have been expressed about possible long-term adverse effects of inhaling a growth protein into the lungs.

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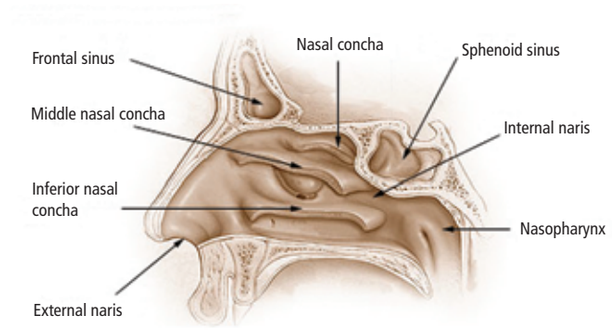
Timothy R Sullivan is a Co-founder, President and CEO of Mystic Pharmaceuticals. He is co-inventor of Mystic's Drug Delivery Technology Platforms. Over the past 30 years, Mr Sullivan has played a principal role in creating and growing companies in life sciences, software technology, energy and management consulting, two of which have been acquired by major corporations. He has served as a planning and technology commercialisation consultant to NASA at the Johnson Space Center and was a co-founder of the SBIR Institute, a technology commercialisation centre at the University of Houston. Mr Sullivan holds an MSc in future studies from the University of Houston and an undergraduate degree in business and physics.

Kurt L Berens is a Senior Scientist in Programme Development at Mystic Pharmaceuticals and has been involved in pharmaceutical and medical device research and development for more than 25 years. He was previously Vice President of Product Development at CytoGenix, Inc., and additional industry experience includes programme management at Texas Biotechnology Corporation. Mr Berens has made contributions towards US Food and Drug Administration approval of the following medical device and therapeutic drug products: GALILEO® Intravascular Radiotherapy System and GALILEO Centering Catheter; Argatroban®; EU, Canadian and Australian approval of Thelin®. He conducted research in pharmacokinetics and drug delivery systems as a graduate student at the University of Houston College of Pharmacy and as a contractor scientist at NASA's Johnson Space Center.

Figure 1: The Nose and the Nasal Cavities



Source: US National Cancer Institute.

Physiological/Anatomical Considerations

One of the most fundamental factors to consider in effective transnasal drug delivery is the tortuosity of air-flow paths through the complex human nasal passage. The nasal passage consists of several functional regions.[3] When a drug-containing aerosol enters the nostrils, it encounters the nares – cone-shaped airways that rapidly decrease in diameter. Within about 2cm of the nasal entrance, the two airways reach a minimum area – the nasal valve or ostium, measuring about 10x2.5mm. Immediately beyond the ostium, the airway becomes significantly larger – particularly vertically, but also laterally – and enters the nasal chamber containing turbinate (nasal concha) structures. The passages are separated down the middle by a narrow septum that extends from the nasal floor to the top of the passage, where the olfactory region is located. The three turbinates (conchae) protrude from the outer nasal walls, forming a complicated airway cross-section (see *Figure 1*). The unusual thickness of the air passage is such that an aerosol passing through this region is within 1mm of a wall. The convoluted walls of the turbinates are supplied with serous fluids from an extensive network of submucosal blood vessels covered with ciliated cells and mucus supplied by goblet cells and glands. Beyond the turbinate region, which is approximately 4cm long, the septum terminates and the two airways merge into the nasopharynx, a downward-curving channel of elliptical cross-section leading to the oropharynx. The length of the nasal passage from the nostrils to the oropharynx is approximately 13cm. Studies show that aerosol particulates deposited in the anterior nasal passage clear more slowly than those deposited on the turbinates or the nasopharynx. Studies have shown that few particulates larger than 50µm will enter the nasal passage in normal inspiration,[5] while particulates smaller than 1µm have good deposition in the nasal mucosa. Soluble particulates – such as those present in an aqueous drug aerosol transnasal discharge – deposited on the nasal mucosa are accessible to the underlying cells, and clearance times of over 15 minutes have been observed. Simulation modelling studies on nasal spray deposition in the human nasal passage have been conducted.[6]

Studies show that aerosol particulates deposited in the anterior nasal passage clear more slowly than those deposited on the turbinates or the nasopharynx.

Ancillary Advantages

As discussed briefly above, the advantages of transnasal drug delivery over conventional oral drug delivery include: the absence of drug degradation produced by the acidic environment of the stomach and the digestive hydrolytic enzyme activity in the gut; the avoidance of nausea or vomiting that can occur when taking oral medicines; the bypass of the blood–brain barrier; and a faster onset of action of the drug due to its more rapid uptake. Because of the potentially greater bioavailability of a drug in a shorter time via the nasal mucosa compared with the oral route, considerations may need to be given to using lower doses of a drug than when the drug is administered orally. This can be an especially important consideration for drugs with a narrow therapeutic index.

The advantages of transnasal drug delivery versus administration via intravenous, subcutaneous, intramuscular or any other route are even more obvious. Transnasal drug delivery is arguably less invasive and certainly much easier than injection. Additional potential advantages for transnasal administration over drug administration by injection are:

- enhanced patient compliance;
- an elimination of the possibility of injection-site injuries;
- reliable drug self-administration by the patient, decreasing the need for drug administration by medically trained personnel;
- an overall decrease in treatment costs to the patient;
- greater ease of use compared with giving an injection; and
- elimination of the sharps disposal factor associated with syringe needle injections.

Patient compliance is a critically important issue and represents one of the most frustrating problems for medical professionals involved in patient care: the lack of health improvement in patients who do not take their medications when they are supposed to. As stated so accurately by former US Surgeon General Dr Koop, "Drugs don't work in patients who don't take them." Due to the ease of self-administration when using transnasal drug delivery, this mechanism can represent an important advantage for patients by improving compliance.

Criteria for Effective Drug Delivery

For successful and effective transnasal drug delivery, accurate targeting of deposition sites within the nasal passage is necessary. In this regard, device designs and dose delivery must be precise and accurate; this is achieved by controlling and stabilising the spray plume geometry through optimum device design. The amount of dose delivered must be consistent between doses. Device design and performance should be considered to minimise the amount of drug that escapes the nasal passage and reaches the oral cavity for

deposition in the lungs or stomach. Furthermore, each actuation from the device should be through a new aerosol nozzle in order to avoid the potential for bacterial contamination and cross-contamination between subsequent doses when using a multidose device. It also is recommended that drug formulations do not contain preservatives or additives that can present potential health-quality issues. Drug preparations for intranasal delivery can be readily prepared and stored with excellent stability without the need for preservatives. For multidose intranasal drug delivery devices, the incorporation of a dose-counting mechanism is generally considered both user-friendly and useful for ensuring medication compliance. Above all, the drug formulation used in transnasal drug delivery devices must be evaluated to validate its continued stability and sterility under device usage and storage conditions, and evaluations need to be conducted to determine the bioavailability and bioequivalence of the drug delivered by the device.

Drug Applications

While certain criteria must be satisfied and maintained, drug applications for transnasal delivery appear to be almost endless. Candidates range from simple drugs (as they move from patent application to generic eligibility) to new innovator-developed simple drugs, to novel applications, to the rapidly growing market for biotechnology-derived drugs such as vaccines, other peptide- and protein-based pharmaceuticals and nucleic-acid-based drugs.[7–9] Examples of the variety of drugs currently in development as transnasal products include insulin, sumatriptan and morphine gluconate, among others. There is, in addition, a variety of drug candidates in various stages of clinical evaluation.

Key to the effective transnasal delivery of drugs is the development of effective drug delivery device designs.[10,11] In order for these devices to be effective and broadly utilised, consideration must be given to the design of device platforms that are capable of consistently generating a drug-containing aerosol with an appropriate plume geometry in terms of a stable particle size distribution that can be efficiently deposited and absorbed by the nasal mucosa for effective drug update; reproducible, providing a high and acceptable consistency of drug delivery; able to provide a sterile drug aerosol; and reasonably low-cost. As such, single-dose devices should be deposable; in multidose or refillable devices the delivery port should be unique to each dose and, to avoid possible cross-contamination, should not be used for more than a single dose. Another important factor is that such devices should not be capable of being repurposed for use with illicit drugs, a factor of high concern to the FDA.

Since there are limitations to the use of popular nasal spray bottles and since their repeated use has been reported to cause nasal irritation, reducing patient compliance, several drug device designs have been developed that provide superior delivery for intranasal drug delivery. Such designs are generally based on the delivery of a controlled fine spray or mist to the nasal passage. Two of these – GSK's Imitrex device and Kurve Technology's ViaNase device – use unit dose ampoules to deliver a single dose of the drug solution in the form of a fine mixed aerosol mist to the nasal passage of a patient. Both are portable devices that can be hand-carried by the user, but cost can be a consideration for patients requiring repeated medication. The GSK Imitrex device is intended to be discarded after use, while the Kurve device will accept single additional ampoules for multidose applications. Since a patient utilising the ViaNase device places the device against the nose for each dose, the device should not be shared between patients. One potential concern for the Imitrex device is that discarded devices may have the potential for being repurposed unless destroyed. For delivery of the drug solution, the Imitrex device is powered by the user depressing a piston, while the ViaNase device requires batteries or a power supply.

The Versi-Doser™ is a new, advanced technology design for intranasal drug delivery developed by Mystic Pharmaceuticals, Inc. The Versi-Doser intranasal system is a single-dose disposable device with a single moving part. It is elegantly simple in design, yet is capable of providing accurate and precise delivery of pharmaceuticals or biologics in a controlled drug aerosol plume geometry that optimises maximum delivery to the nasal passage for efficient mucosal uptake. Mystic is also developing intranasal devices for preservative-free, single-unit dose and multidose delivery that cannot be repurposed after use. In multidose device designs, each dose unit has its own independent drug delivery port, thereby ensuring a sterile application for each dose application.

Conclusion

Transnasal delivery of therapeutics is an exciting and challenging area of pharmaceutics that is undergoing a renaissance. Advances in formulation science[12] are providing enhanced methods for delivering a variety of small and large drug molecules and biologics that were not previously considered as candidates for transnasal delivery. Significant improvements in delivery device technology, including the ease of self-administration, coupled with a significant potential for reduction in the unit cost of new devices, will open markets previously not possible due to cost-prohibitive commercialisation strategies. Next-generation devices will provide geriatric and paediatric patients and the public at large with more cost-effective, user-friendly products for medication delivery. These devices will also be safer and more environmentally responsible by reducing the concern for potential contaminated sharps and biohazardous waste that was sometimes associated with earlier devices. ■

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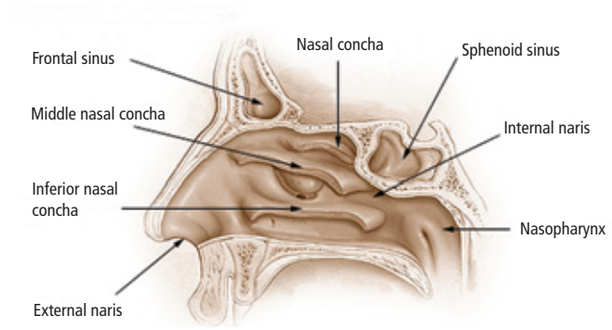

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