THE NASAL SPRAY PUMP MARKET

Approximately 70% (worth $254 billion) of drugs are administered orally to patients, and 2% (worth $6 billion) are administered via the nasal route (Figure 1). Within this 2%, the treatment of allergic rhinitis contributes to one-third, with a $2-billion market value in 2001 with a 10% annual growth. Decongestants and other treatments (including systemic therapies) complete the remaining $4 billion.

The nasal market can be divided into over-the-counter (OTC) and Prescription (Rx) medications. OTC nasal drugs mostly use non-metering devices (the delivery dose is approximate, i.e., squeeze bottle, droppers). In contrast, the Rx nasal drugs use metering devices (the delivered dose is accurate). Using Nasal Metering Drug Delivery Devices, either Multidose or Unit-dose, the following two types of actions can be achieved:

- Local delivery to target specifically the nasal mucosa.
- Systemic delivery of the active drugs as a non-invasive alternative to injection and an alternative to oral treatments to avoid the GI tract.

THE NASAL SPRAY

How Does It Work?
The Nasal Metering Drug Delivery Device (Multidose or Unit-dose) produces a spray of expelled formulation (most of the time liquid), which is directed into the nasal cavity. For a local treatment, the drug produces a local effect within the nasal mucosa. For a systemic delivery, the active ingredient goes through the nasal mucosa and reaches the general blood circulation via numerous capillary vessels present underneath the mucosa. In this case, the nasal cavity (Figure 2) is used as a portal of entry into the blood stream.

Main Advantages
The nasal route for drug administration has significant advantages over the injection and the oral routes.
For example, compared to an injection, nasal devices eliminate the pain and the fear associated with the needle. Delivering a drug via the nose also has the following benefits:

- Easier than giving an injection, thus it may enhance patient compliance.
- Decreases needle injury occurrences.
- Does not necessarily require trained persons for the administration, thus decreasing the total cost of the treatment.

When compared to the oral route, nasal devices have other advantages:

- Elimination of gastric and hepatic drug degradation.
- Avoidance of vomiting after swallowing the drug (eg, during migraine crisis).
- Fast onset of action.
- Fewer side effects due to the potential reduced dosage of the drug.

**Which Devices?**
Instead of the traditional injection that avoids the oral route of administration with proteins and peptides, two non-invasive drug delivery systems for the nasal route are available and already used: the Multidose and Unit-Dose Metering Spray Devices.

Multidose Metering Spray Pumps are specially suited for repeated administrations and can provide numerous doses (typically 50 to 130 mL). Typically, such devices are used to treat chronic diseases. Unit-Dose Metering Spray Devices are specially suited for single administration. These devices are typically used for crisis treatments (ie, pain management) and single-dose delivery (ie, vaccination) and can accommodate liquid formulation, powder formulation, or a mix of both.

**Which Therapies?**
The nasal route of administration is ideal for treating local diseases (Figure 3a), such as allergic rhinitis and nose congestion. In these cases, the common drugs used include steroids, decongestants, saline solution, etc. The nose is also the entry to systemic delivery (Figure 3b) for numerous drugs and different therapies for a variety of diseases. Among these therapies and diseases, hormone replacement therapy (Oestradiol), osteoporosis (Calcitonin), pain management (Butorphanol, Sumatriptan, and Zomipritan), smoking cessation (Nicotine), enuresis (Desmopressin), and motion sickness (Metoclopramide) are already marketed with a Metering Nasal Spray Device.

More drugs targeting other therapies and diseases will soon join the increasing list of marketed products for systemic delivery using the nasal route, such as drugs to treat Central Nervous System disorders (Parkinson and Alzheimer diseases). Another example is nasal vaccination. Mucosal vaccines elicit not only good local immune protection, but also a systemic response similar to that of injection. A nasal flu vaccination could be launched in time for the next flu season.

**Scientific & Cultural Limits**
The nasal route of administration also has limitations. Both scientific and cultural limits can be attributed to this route. To avoid pain and discomfort, a nasal formulation should be of relatively low volume (approximately 70 to 100 mL) and have a pH close to the physiological one. The mucociliary clearance, which is a natural and essential function of the nose, goes against extended drug diffusion from the surface to the nasal mucosa. Such clearance sweeps any particles up (either dust, germs, or medicine) after few minutes.

Finally, the biggest scientific limit to achieve systemic delivery most likely consists of the molecule size. The nasal mucosa can only accept relatively small molecules across its membrane. Absorption decreases significantly with molecular weights higher than 1000 Daltons. Above 3000 Daltons and without absorption enhancers, the bioavailability is rather low for this route to be of great interest. Cultural limits can also be a barrier to the use of the nasal route. Certain people can be reluctant to introduce a device and spray into their nostrils. Others can have doubts about the real efficacy of such nasal drugs.

**NEW TRENDS & UNMET NEEDS**

**Ergonomy**
These days, medication and health not only go with therapeutically effective and safe molecules, but also with the comfort of their dispensing systems. Not only should a delivery system help a patient accept its treatment, but it should also facilitate
the compliance with it. Hence, ergonomics should be applied to nasal device design to make them attractive and user friendly. For example, a side-actuation triggering mechanism (Figures 4 and 5) decreases the actuation force and allows the following:

- A better grip, reducing risks of hurting oneself during instillation.
- Discreet usage while in public.
- Intuitive handling.
- More accurate delivery due to a better orientation.
- A wider population use of nasal devices (i.e., children and elderly friendly).

Ergonomics can also include specific design and customization to accommodate the labeling and product differentiation.

**Preservative-Free Systems**

Preservatives are commonly used in drug formulations. Their advantages are obvious, and they are generally well tolerated. However, when the formulation is delivered directly to the nasal mucosa, some adverse effects may occur due to the preservative, particularly for chronic use. In this case, preservatives can irritate the mucosa, causing some unpleasant itching, but more seriously, they can slow down or even stop the mucociliary clearance, which is essential for the protection of the upper airways. To reduce the inherent preservative risks, regulatory bodies have started to identify and ban such preservatives. This past summer, the German Regulatory Authorities (BfArM) launched a ban on Benzalkonium Chloride (the standard preservative for nasal formulation) in all medications in Germany. This represents more than 300 pharmaceutical products, including 98 nasal products. Preservatives can also make the work of the chemist more difficult by generating some instabilities or by modifying the smell and taste of the formulation, which is not desirable. To help formulation experts reduce or eliminate the preservatives from nasal spray formulations, some drug delivery device manufacturers have successfully developed specific multidose spraying devices, which provide protection, thus making the use of preservatives unnecessary. These devices are based upon the following two main principles:

- Metering Spray Pump working as a closed system: (Aerodiol® from Servier, Nezeril® from Astra Zeneca, and Otrivin® from Novartis). Unlike conventional Metering Nasal Spray Pumps, the closed system does not allow air to enter into the container, thus preventing contamination from airborne germs.

- Metering Spray Pump working with a filter: In this system, the venting air is sucked through a filter assembled inside the pump, which eliminates the airborne germs and keeps them out of the container.

To provide a complete protection of the formulation, specific nozzles are designed to prevent contamination of the formulation trapped in the dead volume of the actuator. Basically, the following two principles can be used:

- A mechanical protection of the dead volume of the nozzle, which opens only when the internal pressure of the liquid increases. When the dose is delivered, the nozzle seals back.
- A chemical protection of the dead volume using a bacteriostatic material (generally silver derivatives or ions) either included or coating parts of the actuator.
Unit-Dose Spray Devices deliver one or two sprays (one per nostril) using a syringe principle: the formulation is pushed out via a plunger from the device. For injections, Unit-Doses can be produced and filled in an aseptic environment or sustain terminal sterilization. Therefore, Unit-Doses can also deliver preservative-free formulations.

**Micro-Electronics & Telemedicine**

We have seen that Metering Nasal Spray Devices can be user friendly and contribute to better patient compliance. Time is ticking until such devices also take advantages of micro-electronics to allow for effective telemedicine. Electronic prototypes (Figure 6) are already featuring new possibilities, such as data transmission, lock-out systems, treatment monitoring, etc.

**SUMMARY**

The nasal route is an already proven alternative method of administration for both local and systemic treatments. Metering Nasal Spray devices are constantly evolving to provide even better solutions to comply with the healthcare and ergonomic needs of the patient.

**REFERENCES**

1. Arthur D Little 2000