Nasal drug delivery devices: Past, present and future device innovations for the would-be product developer

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Abstract

The nasal route of drug administration is a versatile dosing approach that has been increasingly adopted in recent years, as it can provide patient-friendly, non-invasive access to the body. Both systemic and local nasal applications require a delivery device. The main roles of the device are assuring patient compliant, safe and efficient drug delivery to the target site while ensuring formulation stability over the use life of the product. From a commercial perspective, a device may also incorporate unique features that can contribute to a strong intellectual property position and provide differentiation from competing products and therapies. The article will discuss technological innovations in nasal delivery devices that may lead to commercial success.

Introduction

The respiratory route of administration encompasses drug delivery to the lung or nasal cavity. Historically, the prevalence of locally-acting asthma and COPD products delivered to the lung led to them dominate thinking on respiratory administration. More recently, stringent regulatory requirements and high development costs associated with pressurized or dry powder formulations and devices have been depressing interest in pulmonary administration and creating more opportunity for nasal administration, which can look more manageable in comparison.

The nasal route provides an effective method of drug administration. A broad range of topical decongestants, antihistamines, corticosteroids and other remedies are currently available. Some drugs that are administered intranasally are able to enter the systemic circulation and provide a rapid onset of action. In particular, pain relievers like fentanyl or butorphanol are examples of products providing a fast therapeutic effect to meet a clinical imperative.

As the range of nasal drugs increases, innovative formulations and devices are garnering attention. For nasal, as well as pulmonary drug applications, delivery devices have a fundamental impact on the efficacy of a drug. The device is more than primary packaging to contain and administer a formulation; it is a tool, operated by a patient, to transport medication to the target site. A device usually contains multiple components constructed from numerous materials interacting in mechanically-complex ways, forcing device developers and manufacturers to carefully evaluate innovative technological features prior to introduction.

Commercial considerations

The global pharmaceutical market is worth close to one trillion US dollars,[1] with nasal products accounting for about 8 billion dollars (nearly 1%). Growth in nasal products is relatively high compared to other routes of

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administration and some nasally-delivered products are in direct competition with orally delivery forms, such as with the antihistamine, azelastine.

In the past, oral products have dominated the allergy market but there is now a significant shift towards nasally-applied treatments. This trend probably reflects growing acknowledgement of the benefits of direct administration to the target site as well as the commercial imperatives associated with generic competition and ethical to over-the-counter switches in oral products. Combined with a lack of new molecules and innovative formulation options, nasal delivery of an established drug in a new device is attractive in terms of strategic position, product differentiation, time-to-market and financial investment.

The nasal mucosa also remains of interest for systemic drug delivery capturing close to 30% of the overall nasal market. This contrasts with lung delivery, which is dominated by locally-acting drugs. This difference could be caused by different regulatory requirements and development complexities or reflect the increased difficulty of getting drug-containing particles into the lung, which is well protected from foreign particle inhalation. One of the functions of the nose is to trap particles before they reach the lung. Anatomical and physiological features that facilitate this function make the nose less vulnerable to irritation and more amenable to drug capture and retention than delivery to the lung.

The nose is also readily accessible and many patients are familiar with and accepting of the concept of nasal sprays. This is the basis of the "patient-friendly" concept sometimes attributed to nasal delivery. For instance, patients may prefer to receive calcitonin to treat osteoporosis via convenient self-administration at home, rather than an injection that necessitates a physician office visit.

Other applications of systemic delivery via the nose include pain management, which requires a fast onset of action with a similar kinetic profile to injections. Various migraine treatments have been available as nasal sprays for years, as have opiates for breakthrough and postoperative pain management. The latest nasal example of systemic delivery to the central nervous system is intranasal midazolam[2] used as a sedative and anxiolytic agent for patients undergoing dental, diagnostic and surgical procedures or gastrointestinal endoscopy. It is also indicated for acute seizure management.

Delivery systems

Traditional nasal delivery systems were nasal drops, pipettes or squeeze bottles. The use of pipettes with nasal drops might work for certain drugs and formulations. However, due to inconsistencies with reliability, dosing precision and repeatability, their safety and and efficacy have been controversial. In adults, drops mostly deliver drugs to the floor of the nasal cavity, where they are rapid cleared by cilia towards the throat. Squeeze bottles generate a coarse spray into the nasal cavity and are generally used for moisturising saline solutions where dosing precision is not critical. These systems are, however, often unpredictable in terms of dose volume and spray performance and they necessitate use of chemical preservatives to prevent contamination of the bulk following first use. An example is the Ocean Nasal Mist (sodium chloride), which contains two different preservatives.

Mechanically-generated sprays and other dispensing systems able to deliver suspensions, creams, ointments, gels and powders to the nose are now more common. Early metered dose, mechanically-actuated, aqueous nasal sprays, such as Dexa Rhinospray from Boehringer Ingelheim, were developed and marketed in the mid-1970s for treatment of allergic rhinitis and are still on the market today.

A modern developer's portfolio would now contain devices and actuators for other formulations, which opens the door to nasal delivery of moisture-labile biologicals or drugs needing prolonged retention in the nose.

In general, mechanical dispensing systems can be divided into multi-dose and unit-dose systems. Multi-dose systems consist of a container sealed with a mechanical pump dispenser, designed to deliver a certain number of doses. In contrast, unit-dose systems are disposable devices for one-time applications or emergency treatments.

There are different types of multi-dose pumps on the market but they operate on the same basic principle. The user applies force to the pump; the resulting hydraulic pressure, acting on the filled and closed metering chamber, causes the incompressible liquid within to be extruded through the path of least resistance towards the nozzle. The patient-applied energy acts at the nozzle to break the formulation into a mist comprised of droplets. While droplet size will vary depending on the formulation, median-sized droplets would generally be 30-100 μm.

The most important characteristics that delineate the performance of a dispensing system are the metering volume, the spray angle, the spray pattern and the particle size distribution which, combined with the drug concentration, define the dose and can influence the location where it is likely to deposit. These operate in concert with formulation parameters, such as viscosity, thixotropy, surface tension and density, to define plume characteristics. Modification of the functional design of the nasal actuator makes it possible to adjust the spray performance to meet specific requirements.

For local applications in the nose, product designers typically seek to keep the fraction of extremely small particles low to avoid partial inhalation of the drug dose into the lung. Typical dose volumes per nostril are 100 μl for adults and around 50 μl for infants and children.

Preservative-free nasal products

Nasal preparations are usually microbiologically preserved to prevent contamination of their contents after use via the nasal actuator or aerating vent (which prevents negative pressure developing in the container as

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the formulation is used). In some European markets, preservatives are seen as having a negative impact on the cilia of the nasal epithelium and occasionally regulatory authorities have advised omission of preservatives, if possible.[3] This has driven a trend towards preservative-free formulations, which have been commercialized in South America and Europe.

From the multi-dose device perspective, an unpreserved formulation requires a different approach in which responsibility for non-contamination shifts from the formulation to the primary packaging. Device developers and manufacturers have implemented two basic approaches to prevent ingress of microbes. One is the integration of a bacteriostatic agent into the device, such as silver, which is widely used in Europe. For example, a silver coil can be integrated in the tip of a device to protect the critical area of the actuator's orifice and efficiently inhibit bacteria growth. The second principle is based on mechanical barrier properties, where a spring-loaded pin mechanically seals the orifice at the end of the nasal actuator during the periods of non-use. Only during formulation dispensing is the orifice open and able to generate and release spray (Figure 1). Both protection principles are practiced in the market, in part, because company-specific procedures have been developed to evaluate and demonstrate their ability to resist contamination following patient use.

The process for evaluation of preserved multi-dose formulations is clearly specified in many pharmacopoeias and guidance is available for sterile, unpreserved unit-dose delivery systems. However, there are no official testing protocols for unpreserved multi-dose nasal sprays in any pharmacopoeia. For this reason, a committee of experts in Europe[4] is currently charged with advising whether such delivery devices must be regarded as a new dosage form covered by a new chapter and specifications, or whether it is appropriate to augment the chapter on sterility and microbiological quality in the European pharmacopoeia to address them.

The generation of a valid and meaningful test protocol to assess non-contamination must be based on consideration of a real-user scenario. A practical approach is illustrated in Figure 2.[5] An actuation of the device in a bacterial suspension simulates the insertion and administration of a nasal spray into the nasal cavity. Multiple contamination cycles with several actuations per day are followed by an appropriate incubation time to allow microbiological integrity of the complete package to be thoroughly challenged.

Sophisticated systemic delivery of peptides, which are by nature sensitive to microbial contamination, is also in development pipelines, as are simple moisturising saline solutions for daily use.[6] Devices in the preservative-free nasal delivery market in Europe are distinguished by the CE mark of conformity. Most of these nasal sprays are based on saline solutions and fall under the category of moisturizers. These products are sold almost solely over-the-counter and can be brought to market in a short period of time, perhaps six months. A recent development in a CE-marked nasal spray is incorporation of the gelling agent carrageen. Several clinical trials have asserted its antiviral effectiveness against common cold viruses.[7]

Figure 1

Mechanically-protected, preservative-free, nasal pump system

Unit-dose systems

Unit-dose, preservative-free nasal products are conceptually easier to develop and can be designed to deliver one or two sprays. The first product to utilize this approach was Calsynar from Sanofi-Aventis, which delivered calcitonin as a preloaded, once-daily dose. Some years later, two different drug products packed in unit-dose systems for nasal application for the treatment of migraine reached the market, Imigran from GSK and Zomig from AstraZeneca.

Today, an increasing number of nasal administration projects have systemic drug delivery as their goal. Many of these disposable devices are appealing, due to their ease of use in emergency situations by inexperienced or impaired users. Development activities linked to unit- and bi-dose systems focused on vaccination are also appealing. This concept is now established following the first nasal influenza vaccine launched some years ago, Flumist from MedImmune, now AstraZeneca. Its primary benefit was combination of a mucosal antibody response in the nasal cavity followed by a response in the systemic system.

Unit-dose systems require dedicated filling technologies and are more expensive on a cost-per-dose basis. Consequently, it is essential to anticipate this to maximize the chance of commercial success. A recent development is a disposable nasal unit-dose and bi-dose delivery device that combines optimized commercial and technological

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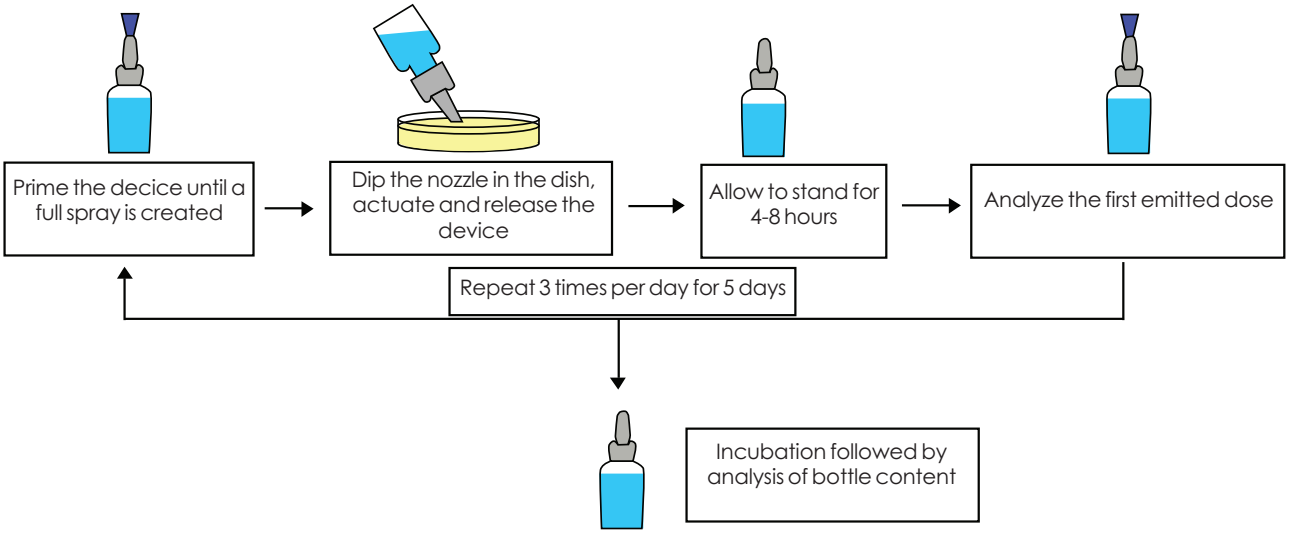
Figure 2

Illustration of a microbiological protocol to assess non-contamination of preservative-free nasal delivery products



characteristics. In contrast to existing disposable unit-dose systems which utilize various construction materials, the new device consists of a minimum number of parts each made solely of innovative polymeric materials. In addition, device performance can be easily adapted to the physical properties of a formulation and to anticipated patient requirements. A purpose-designed filling technology makes this an attractive disposable nasal device platform (Figure 3).

Figure 3

A nasal unit-dose spray

Summary

Nasal drug delivery is an attractive, growing niche in the drug delivery market, in part because these devices can confer added value compared to generics and clinically are able to deliver fast onset with non-invasive administration of systemically-acting drugs, including biologics. Development efforts are focusing on reformulation and repackaging of successful, existing systemic-acting drug products. The regulatory pathways in Europe and in the US are increasingly clear. This author foresees increased penetration of the market by preservative-free products. Modest investment costs and relatively short product development times are attractive and conducive to early product launches. Generally speaking, nasal delivery is very versatile mode of administration for pharmaceutical and non-medicated products.

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