

Nasal and sublingual spray delivery devices: Market opportunities and unmet medical needs

A brief look at new options

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Uses and advantages of nasal drug and sublingual spray delivery

Nasal drug delivery devices have been in use for more than 40 years and are a widely recognized route for topical treatment of local diseases in the nasal cavity such as allergic and non-allergic rhinitis and nasal congestion.¹

In addition, nasal drug delivery has emerged as a successful option for needle-free delivery of systemic drugs where rapid absorption and onset of action are necessary, for instance, in pain management, migraine crisis and opioid overdosing episodes.¹

The advantages of nasal mucosal and sublingual spray delivery are well known¹ and include non-invasiveness (compared to injections); easy accessibility for administration; use of a relatively large, highly vascularized, mucosal surface area; high systemic bioavailability for some drugs; avoidance of hepatic first pass metabolism and the potential for rapid onset of drug action. Other attractive features are the potential for increased patient compliance and improvements in pharmacokinetic profiles.

Nasal delivery devices also have limitations that must be considered. These include limited absorption for higher molecular weight compounds (greater than 1,000 daltons); concerns about a patient's ability for nasal clearance and the influence of patient nasal physiology (due to colds, allergies, etc.); and difficulty in reaching some targeted areas of the nasal anatomy.¹

Nasal drug delivery holds further promise and this article will look at a variety of unmet medical needs and market opportunities it could address.

Increasing global health care needs

By 2030, there will be 1 billion people over 65 years of age worldwide compared to 600 million currently,² and healthcare must adapt to this changing demography. In addition, healthcare costs are rising globally and there is a growing demand for therapeutically relevant medications that can be developed quickly and at reasonable costs for a variety of diseases and high unmet medical needs. Several obvious adaptations are necessary, including shortened inpatient hospital stays; increased outpatient care; more self-administration of drugs and greater palliative care. Nasal and sublingual spray delivery devices can play a role in these scenarios as they can be easily adapted for elderly patient use from the viewpoint of ergonomics, portability and ease of self-administration.

Unmet needs in CNS diseases

In 2015, the global pharma prescription market was valued at approximately \$1,120 billion US dollars with an impressive 6% growth rate over 2014.³ Within this, the market for central nervous system (CNS) therapy was valued at \$143 billion US dollars.

The CNS market is of interest as it comprises several areas, some with high unmet medical needs, such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, migraine, insomnia, ADHD (attention deficit hyperactivity disorder), anxiety disorders and bipolarism, where non-invasive nasal delivery—in particular unit dose and bidose approaches as opposed to multidose—could prove very beneficial. Although many CNS diseases are of a chronic nature, strong opportunities also exist for acute treatments such as seizures and overdosing episodes.

Figure 1**A unit dose powder device***(Photo enlarged to show detail)***Figure 2****A unit dose liquid device***(Photo enlarged to show detail)*

Nose-to-brain delivery

Another option generating much attention is the possibility of treating CNS diseases by the so-called “nose-to-brain” route. It is well known that only about 1% of existing drugs can pass through the blood brain barrier (BBB),⁴ whose function is blocking molecules it considers harmful or toxic to the brain.

Drugs targeted at the olfactory region in the upper portion of the nasal cavity could be transported to the brain and bypass the BBB, although this is still a somewhat controversial subject.⁴ The olfactory region is difficult to access because of the restricted nasal anatomy, with the turbinates lying in the way. However, much interest and progress is being reported in this area⁵ and specifically designed delivery devices hold promise for finding solutions to this difficult challenge in successful delivery of drugs to the CNS.

Delivery of small molecules; Options for life cycle management

In order to harness the total value of a drug product, nasal delivery devices with their established technology and well-documented regulatory guidelines can enhance product life cycle management (LCM). The LCM strategy is not new. Recently up to 30-40% of the drugs or biologics approved or launched for the first time in the United States were either existing drugs repositioned for new indications, reformulations or new combinations of existing drugs.

With fewer non-biologic new molecules in the R&D pipeline,³ pharma and specialty pharma companies are actively searching for lower-risk development options. Due to this change in market dynamics, numerous opportunities are appearing in the nasal drug delivery area for small molecules to treat unmet medical needs such as Alzheimer’s and Parkinson’s disease. These can often be focused on either LCM opportunities for innovative formulations of established drugs in new devices or on development of known drugs for new applications. This is another area where opportunities can lie for nasal delivery, including unit dose and bidose drug delivery systems.

Preservative-free formulations

Preservatives are used to protect the liquids in nasal spray and liquid sublingual spray formulations from bacterial contamination during storage and use-life. However, typical preservatives such as benzalkonium chloride, parabens and ethylene diamine tetra-acetic acid (EDTA) have been reported to cause damage to the nasal mucosa when used in chronic therapies and have side effects such as hindrance of the ciliary clearing functions within the nasal cavity.¹

Nasal delivery devices that contain dry powders or preservative-free formulations offer opportunities to avoid the use of preservatives and their potential complications. Several options now exist including unit dose and bidose drug delivery spray devices, in both liquid

Figure 3**A bidose powder device**

(Photo enlarged to show detail)

and powder forms. Various technical approaches in devices have been used to provide options for preservative-free formulations including anti-bacterial components (e.g., silver), mechanical tip closures with microbial filters and so-called “bag-on-valve” technologies.

The potential of unit-dose and bidose nasal delivery devices

Common features

Unit dose (single dose) or bidose (dual dose) drug delivery spray devices come in many forms but tend to have common characteristics such as:

- An unpreserved, pre-filled liquid or powder dose in a protective chamber
- Some means of delivering and atomizing the liquid dose or a pre-prepared powder formulation with a particle size suitable for effective nasal dosing
- Usually disposable after usage of one or two doses

Potential benefits

Unit dose and bidose forms can be less complicated to develop than multidose systems. They can also readily be customized for product differentiation, e.g., Zomig® (zolmitriptan) (AstraZeneca) and Subsys® (fentanyl sublingual spray) (Insys Therapeutics). Figures 1-4 show examples of available technologies for unit dose and bidose nasal delivery.

In addition, the industrial filling and packaging processes used in their manufacture are well established and

Figure 4**A bidose liquid device**

(Photo enlarged to show detail)

have been validated, often with off-the-shelf or minimally customized equipment being employed.

These dosage forms can offer a variety of benefits including sterility and “ready for use” in cases of emergency treatment. They generally contain smaller amounts of drug/formulation than multidose units, which may increase their safety and decrease the risk of diversion issues related to controlled substances.

These devices can also provide convenience to patients because they tend to be small, portable and ready for use without the requirement for priming. These characteristics can also aid patient adherence because device use can readily be monitored and doses can easily be counted, while with multidose systems, dose counters may not be readily available so dose monitoring can be more challenging.

Regulatory and human factors expectations

The technical and regulatory expectations for nasal and sublingual sprays have evolved and been clarified over the last few years in both Europe and the United States⁷⁻¹⁰ with other regions such as South America following rapidly. Parameters such as droplet or particle size distribution, spray pattern, dose content uniformity and extractable and leachable profiles are now common expectations for regulatory dossiers. Consequently, drug delivery devices, as well as their corresponding formulations, have evolved to meet the increased requirements of specifications and quality standards.

Today’s regulatory requirements also expect that drug delivery devices undergo human factor analysis (HFA)¹⁰

Sublingual spray delivery: An alternate route of administration for existing device technologies

Sublingual delivery sprays have emerged recently and found success in applications such as the breakthrough cancer pain therapy Subsys[®] (fentanyl sublingual spray) from Insys Therapeutics and Sativex[®] (a cannabinoid medicine for the treatment of spasticity due to multiple sclerosis) from GW Pharmaceuticals.

In sublingual spray delivery, using devices similar to those for nasal administration, drugs are delivered under the tongue to the oral mucosa, which possesses a range of traits to facilitate drug delivery.¹¹ Drugs delivered to

this site can easily move into the bloodstream without having to pass through the gastrointestinal tract and the liver.

Drugs can be considered for sublingual spray delivery if they dissolve rapidly through the oral mucosa. However, pH, molecular weight, lipid solubility and rapid clearance must be considered in order to have an effective product.¹² Because sublingual spray delivery devices are similar to those used for nasal delivery, this can present new market opportunities for manufacturers.

during the research and development process. Unit dose and bidose drug delivery spray devices are well-suited to HFA device improvements. Due to their simplicity and modest size, they generally can be easily optimized, modified and customized with respect to key HFA factors, such as use environment, user influences, device complexity, patient interface and failure modes. Key characteristics such as actuation forces, shape, size, metering volumes, prime-free functioning and lack of containers or bottles for large volumes make these products quick, easy and less complicated to customize.

Applications

Some unit dose and bidose nasal drug delivery spray devices have found their niche with higher-value prescription drugs and vaccines, e.g., PecFent[®] (fentanyl pectin nasal spray) (Archimedes Pharma) and FluMist[®] Quadrivalent (influenza vaccine live, intranasal) (AstraZeneca) intended for single administration or infrequent on-demand use, where greater control of the dose and formulation is of more importance.

One clear advantage of unit dose or bidose drug devices can be exploited in the case of potent or controlled drug substances. In a multidose device, a significant amount of the potent or controlled substance is held in the container and diversion, misuse or abuse of this large quantity of drug could be potentially dangerous. In contrast, a unit dose or bidose spray device can mitigate these risks by providing limited doses of these substances. That feature, combined with careful prescribing by clinicians, can help avoid overdosing or misuse.

A full pipeline

Commercialized unit dose or bidose spray devices are currently on the market or in development to treat an array of diseases such as Alzheimer's, diabetes, epilepsy, migraine, osteoporosis, Parkinson's and hormonal diseases. These devices are also being used for pain management, sleep aids, vaccines and vitamin deficiency. A review of this drug development area reveals that there are more than 100 active projects,⁶ indicating a very busy and full pipeline.

Looking forward

Nasal and sublingual spray drug delivery are proven and successful areas for prescription medication treatment of a variety of health disorders. Changing world demographics, as well as rising healthcare burdens and costs, are expected to drive the market towards innovative drug delivery approaches that can be brought to market faster and at lower cost. In addition, life cycle management opportunities, including repurposing of existing drugs, can include nasal drug delivery. Opportunities to address unmet medical needs in CNS disorders range from Alzheimer's and Parkinson's diseases to schizophrenia and bipolarism. Nasal drug delivery may also provide safe and efficacious opportunities for delivery of small molecules. In particular, unit dose or bidose nasal drug delivery systems can offer important solutions to these outstanding opportunities.

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