Catalent®
INHALATION

Q & A

INDUSTRY TREND: Examining the Emergence of Unit- & Bi-Dose Nasal Sprays

Molecules that are limited by a slow onset of action, a suboptimal side-effect profile, or a complicated administration process, may be good candidates for adaptation to a unit- or bi-dose nasal delivery format. This is especially true for drugs targeting the central nervous system (CNS). Established molecules may also benefit from shorter development timelines and regulatory review cycles.

Nasal spray administration of medicine offers advantages over oral and intravenous (IV) delivery. Catalent's Andrew Samuelsson, Craig Davies-Cutting and Tom Clark discuss the advantages and opportunities of adopting unit- and bi-dose nasal delivery technology.

Featured Experts:

ANDREW SAMUELSSON, PH.D.
Product Manager, Oral & Specialty Delivery

CRAIG DAVIES-CUTTING, PH.D.
Director, Inhaled Products & Technologies

TOM CLARK
Director, Commercial Operations, Inhalation

Q: What are the advantages of the nasal route of administration?

SAMUELSSON: Historically, nasal sprays have typically been associated with treatment of local conditions such as allergies/rhinitis. However, over the last 10+ years there has been an increasing focus on nasal administration for the delivery of molecules to the CNS as well as for systemic delivery. Dosing via the intranasal pathway has shown a rapid onset of action, comparable to that of IV administration, with kinetics considerably faster than that of oral delivery[1-3]. Intranasal administration has gained attention as a method to target the CNS since this route provides a practical, non-invasive means of bypassing the blood-brain barrier by leveraging the putative nose-to-brain pathway[4-7].

Relative to IV injection, intranasal delivery offers a similar onset of action, without the associated discomfort or need for administration by a healthcare professional. When targeting the CNS, intranasal delivery can achieve similar drug concentrations in the brain with a significantly lower concentration in circulation relative to IV[3,8], thus likely reducing the prevalence and severity of systemic side-effects seen with high circulating drug concentrations. Unlike molecules transported via the nose-to-brain pathway, those that come from circulation often have difficulty breaching the blood-brain barrier, and it is estimated that 98% of small molecule drugs are unable to pass this barrier[9]. Techniques that forcibly bypass (*e.g.,* intrathecal infusions) or weaken/open the blood-brain barrier (*e.g.,* mannitol injection) can carry

SAMUELSSON (CONT'D):

significant risks[10,11]. Lastly, nasal sprays avoid the risks of needle stick and injection injuries, especially in situations where the patient lacks gross motor control (*e.g.,* patient is having a seizure).

Oral administration is often the preferred format for drug self-administration, but suffers from first pass metabolism, slow onset of action and many of the systemic side effects seen with IV. Higher doses are typically used to offset the impact of hepatic metabolism, which can lead to gastrointestinal discomfort or toxicity, and ultimately limit an oral drug's development path. While a portion of a nasal spray will also end up in the gastrointestinal tract, the concentration of a nasally delivered drug is typically orders of magnitude lower than that needed for comparable oral delivery, thus significantly mitigating the risks of side effects[12]. In general, intranasal delivery can overcome a number of challenges associated with oral and intravenous administration, especially for CNS conditions (see Table A).

	INTRANASAL	ORAL	INTRAVENOUS
SPEED (ONSET OF ACTION)	++	-	++
CONVENIENCE	++	+	-
MINIMAL SIDE EFFECTS	++	-	+
PATIENT COMFORT	+	++	-
AVOIDANCE OF FIRST-PASS METABOLISM	++	-	++
SELF ADMINISTRATION	++	++	-
DOSE ACCURACY	++	+	++
MINIMIZES API NEEDED	++	-	++

The potential for nose-to-brain delivery as a targeted route of drug delivery is great; however, there are a few challenges, such as a limited understanding of the nasal mucosa[13], avoidance of immunogenicity through optimized formulation[13], and patient-to-patient variability in nasal passage architecture or obstruction. While systemic and enteric side effects are generally lower with nasal sprays, patients can experience throat irritation, nasal discomfort and other side effects of the nose, throat or eyes[1]. Furthermore, the pathway may not work for all molecule types, and device manufacturers and formulators continue to look for ways to maximize residence time and absorption at olfactory receptors and the nasal mucosa, respectively, and minimize mucociliary clearance into the stomach.

Beyond nose-to-brain, intranasal administration can also be used for systemic drug delivery. The nasal mucosa is well-vascularized and thinner than the intestinal mucosa, allowing for rapid drug absorption directly into the bloodstream, bypassing intestinal and hepatic metabolism. Similar to that seen with nose-to-brain, this route allows for rapid onset of action, non-invasive delivery and the potential for lower dose requirements relative to that needed for oral administration. However, compared to IV, higher doses are needed and one should be cognizant of potential accumulation in the brain via the parallel nose-to-brain path.

Catalent®
INHALATION

Q: How are unit- or bi-dose nasal sprays different than traditional multidose nasal sprays? What are their advantages?

SAMUELSSON: Unit-dose and bi-dose nasal sprays are disposable and – compared to multidose – have a smaller profile, are sealed and less likely to leak in a purse or backpack, and do not require priming prior to use. These small differences improve convenience and may ultimately improve patient compliance, especially for conditions where need for treatment is infrequent to the point where carrying a larger multi-dose is impractical.

In addition, unlike multi-dose sprays, unit-dose nasal sprays can typically be preservative-free. For products containing a controlled drug substance, unit- and bi-dose nasal devices limit the ability for abuse due to the use of sealed vials with set volumes, low drug concentrations and drug formulations already intended for rapid uptake. Unit- and bi-dose devices also provide precise drug delivery volumes, reduce risks from microbial contamination and are intrinsically tamper-evident. Without the need for priming, they also result in less wasted API, making them more suitable for costly APIs.

Q: What are the typical applications of unit- and bi-dose nasal delivery devices? What kind of treatments are they suitable for?

DAVIES-CUTTING: These nasal devices are good choices for a number of CNS applications, including Parkinson's disease, opioid abuse, epilepsy/seizures and pain applications, such as acute/breakthrough pain, cancer-related pain, chronic pain and migraine. Other conditions such as diabetes-related hypoglycemia and paroxysmal super-ventricular tachycardia are also target conditions.

Current medications for these conditions, reformulated for intranasal administration, may benefit from either improved speed of action, non-invasive delivery or a reduced side-effect profile, and can potentially be adapted for unit- or bi-dose nasal delivery with shorter development timelines and regulatory review cycles.

Q: What are the differences between unit- and bi-dose nasal devices?

CLARK: The applications of unit- and bi-dose devices are largely the same; the choice between unit- and bi-dose is driven by the volume needed to administer the required dose. Unit-dose devices are suited to administration of volumes up to 100µL, and bi-dose for volumes of 100-200µL. A unit dose product typically has a fill volume of 125µL to enable delivery of 100µL of formulation. A bi-dose applicator has a fill volume of 250µL for delivery of 200µL of formulation. Catalent has commercial- and clinical-scale manufacturing equipment for both unit- and bi-dose nasal formats.

Catalent®
INHALATION

Q: Is unit-dose only suited to liquid?

CLARK: No, unit-dose powder devices also exist. In fact, the first nasal product in a unit-dose powder device was recently approved and is manufactured by Catalent.

Currently, the dry powder variant is only available in a unit-dose format, but carries many of the same advantages as the liquid unit-dose variant such as preservative-free formulation. The powder variants can also administer larger doses and have the potential to be more stable than their liquid counterparts in scenarios where a liquid formulation does not provide adequate stability.

Q: What is driving the shift towards unit/bi-dose nasal for manufacturers and customers? What are some of the trends in the industry?

CLARK: The shift is largely a result of the benefits mentioned above for acute/CNS therapies: an increased focus on controlling dose accuracy, non-invasive delivery and preventing abuse, especially in light of the opioid epidemic. Drug makers are also interested in this space as unit- and bi-dose nasal sprays are more lucrative than traditional multi-dose sprays. Currently, nasal liquid products make up the majority of all inhalation products in development, largely driven by pharmacological and manufacturing advantages as well as a surge in nasally delivered vaccines.

Q: What are the key considerations for developing a unit/bi-dose intranasal product? What about formulation development?

DAVIES-CUTTING: The nasal cavity has long been used for rapid and non-invasive delivery. The key to development is ensuring accurate and reproducible delivery as well as effective permeation of the API through the nasal epithelium (*e.g.,* by using permeation enhancers) or extending residence time at the target receptor or nasal mucosa at large (*e.g.,* with bioadhesives).

For solution formulations, there are several key considerations including: API solubility, which can impact potential dose; solution stability; osmolarity, which can impact bioavailability; pH, which can impact solubility or cause irritation; and formulation filling (*e.g.,* micro-dosing liquids into small vials). For filling, viscosity is a critical factor as it not only impacts vial filling and the delivery performance of the spray pump, but also influences residence time of the drug at the absorption site.

For powder formulations, powder flow is an important matter for filling small vials (*e.g.,* micro-dosing). Also, physical stability, and the size, shape and surface properties of the powder are all important considerations, as these elements can all impact the redispersion or aerosolization of the powder and hence the dose delivery performance.

Catalent®
INHALATION

Q: Describe the best practices for establishing the desired quality target product profile (QTPP).

DAVIES-CUTTING: Nasal sprays are drug-device combination products and hence require alignment to the FDA's Code of Federal Regulation section on quality system regulation (CFR820), which ensure that a manufacturer's products consistently meet applicable requirements and specifications. To achieve this, one needs to carefully consider the interplay of formulation, device and process as these are all critical elements controlling the quality of the final drug-device combination product.

The QTPP is a living document, but key elements should include:

TARGET DISEASE	• Identify disease or patient population
REGULATORY STRATEGY	• Territory, NCE/generic, orphan/fast track, etc.
CRITICAL MATERIAL ATTRIBUTES	• API and raw materials control strategies • Device type and control strategy
CRITICAL QUALITY ATTRIBUTES	• Formulation type • Stability (shelf life and storage) • Delivery performance – spray actuation content, delivered dose, droplet/particle size distribution, spray pattern
CRITICAL PROCESS PARAMETERS	• Manufacturing operations and scale

Q: What are the benefits of quality by design (QbD) and how can it be incorporated into the product development process for unit/bi-dose nasal devices?

DAVIES-CUTTING: In addition to embracing the typical QbD product development paradigm described in ICH Q8(R2) for pharmaceutical drug products, there are additional considerations for drug-device combination products that need to be addressed to ensure the design space has been appropriately mapped and controlled.

Specific to unit/bi-dose nasal spray drug-device combination products, key design space questions are:

- Does the unit/bi-nasal device supplier have the appropriate controls (*e.g.,* materials, critical dimensions, etc.)?
- What are the effects of manufacturing tolerances on product delivery performance when the device is married with the formulation? (*e.g.,* micro-dosing of the formulation into the device vial, vial stoppering and product assembly)
- What are the effects of device tolerances on the stability of the drug-device combination product?

Catalent®
INHALATION

REFERENCES

1. Bancke L, Dworak HA, Rodvold KA, Halvorsen MB, Gidal BE. Pharmacokinetics, pharmacodynamics, and safety of USL261, a midazolam formulation optimized for intranasal delivery, in a randomized study with healthy volunteers. Epilepsia. 2015 Nov;56(11):1723-31.
2. Fattinger K, Benowitz NL, Jones RT, Verotta D. Nasal mucosal versus gastrointestinal absorption of nasally administered cocaine. 2000 Jul;56(4):305-10.
3. Westin UE, Boström E, Gråsjö J, Hammarlund-Udenaes M, Björk E. Direct nose-to-brain transfer of morphine after nasal administration to rats. Pharm Res. 2006 Mar;23(3):565-72.
4. Pardeshi CV, Belgamwa VS. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood-brain barrier: An excellent platform for brain targeting. Expert Opin. Drug Deliv. 2013 Jul;10(7):957-72.
5. Kumar H, Mishra G, Sharam AK, Gothwa A, Kersharwani P, Gupta U. Intranasal Drug Delivery: A Non-Invasive Approach for the Better Delivery of Neurotherapeutics. Pharm. Nanotechnol. 2017 May;3:203-214.
6. Jiang Y, Li Y, Liu X. Intranasal delivery: circumventing the iron curtain to treat neurological disorders. Expert Opin. Drug Deliv. 2015 Dec;(11):1717-25.
7. Mittal D, Asgar A, Md S, Baboota, S, Sahni JK, Ali J. Insights into direct nose to brain delivery: Current status and future perspective. Drug Deliv. 2014 Mar;21(2):75-86.
8. Wang Y, Aun R, Tse FL. Brain uptake of dihydroergotamine after intravenous and nasal administration in the rat. Biopharm Drug Dispos. 1998 Dec;19(9):571-5.
9. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. NeuroRx. 2005 Jan;2(1):3-14.
10. Joshi S, Meyers PM, Ornstein E. Intracarotid delivery of drugs: the potential and the pitfalls. Anesthesiology. 2008 Sep;109(3):543-64.
11. Turner JA, Sears JM, Loeser JD. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. Clin J Pain. 2007 Feb;23(2):180-95.
12. Chen TC, Fonseca CO, Schonthal AH. Intranasal perillyl alcohol for glioma therapy: molecular mechanisms and clinical development. Int. J. of Mol. Sci. 2018 Dec;19(12):3905.
13. Gänger S, Schindowski K. Tailoring Formulations for Intranasal Nose-to-Brain Delivery: A Review on Architecture, Physico-Chemical Characteristics and Mucociliary Clearance of the Nasal Olfactory Mucosa. Pharmaceutics. 2018 Aug 3;10(3):116.

more products.
better treatments.
reliably supplied.™

Discover more solutions at catalent.com/specialty
GLOBAL +1 888 SOLUTION (765-8846)
EU 00800 88 55 6178
solutions@catalent.com