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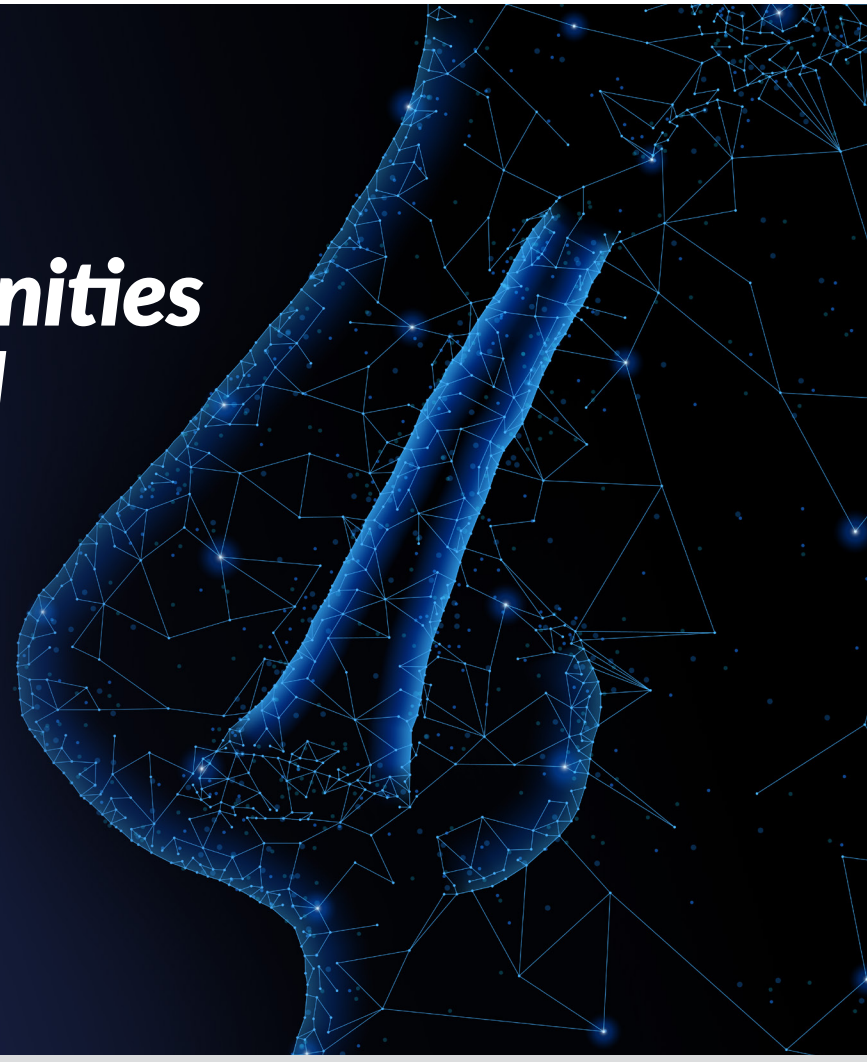
New Opportunities for Intranasal Products: Formulation and Delivery Strategies



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Intranasal Drug Product Development—From Formulation to Scale-Up Manufacturing

Interview with Kiran Amancha, Ph.D., Jan Neelissen, Ph.D., and David Wilcox

Pharmaceutical Technology spoke with experts from Catalent on intranasal drug product development—its benefits, applications, best practices and more.

PHARMTECH: What are some characteristics of active pharmaceutical ingredients (APIs) that make them good candidates for systemic absorption after intranasal administration?

NEELISSEN: In terms of physiochemical properties, APIs should be low-molecular-weight (< 300 Da), non-polar drugs, have good permeability, be active in low doses (< 10 mg) and have good solubility at physiological pH. In addition, APIs that are unstable in gastrointestinal (GI) fluids or have high first-pass metabolism after oral dosing are considered as possible candidates for intranasal administration.

How can physiologically based pharmacokinetic (PBPK) modeling tools help predict drug absorption and guide formulation development?

NEELISSEN: Using the physicochemical properties of the API and

in silico predictions or measurements of key parameters such as permeability and solubility, PBPK modeling can be used to predict fraction absorbed through the nasal mucosa and help determine if the API is a suitable candidate for intranasal delivery. If oral pharmacokinetic data is available, PBPK modeling can be used to estimate the intranasal dose needed to match the systemic exposure following oral administration. PBPK modeling can guide formulation strategy, for example, by determining if the formulation should be solution-based or powder-based by predicting the expected exposure following administration of each type.

What are the benefits of intranasal drug administration? What are typical applications/indications?

NEELISSEN: First, it avoids first-pass loss and avoids degradation in the GI fluid, both of which are potential issues associated with oral delivery. Second, it offers ease of administration and fosters better patient compliance for those with difficulties swallowing tablets. And third, intranasal drug administration ensures rapid drug absorption and quick onset of action. It offers the potential for direct access to the brain via olfactory and trigeminal nerves, thus avoiding the blood-brain barrier in addition to reducing side effects owing to lower systemic exposure. It can be used in treatments for migraines, headaches, break through cancer pain, hormone replacement therapies, smoking cessation, epilepsy, cardiovascular indications and more.

What are best practices for intranasal drug product formulation design?

AMANCHA AND WILCOX: The formulation of a nasal drug product needs to be designed to support the required product performance attributes to achieve the desired release and absorption within the nasal cavity. First, establish if solubility and/or permeability is/are limiting factor(s) of the API's bioavailability. The majority of nasal liquid formulations are aqueous-based and given the high percentage of poorly soluble APIs in development, it may be necessary to select a vehicle or solvent system that enhances the solubility of the API. Solubilizers/surfactants/co-solvents are evaluated to enhance the solubility of the API and should have limited irritant and toxic effects on the local tissues at the levels used in the formulation. If it is a permeability issue, the bioavailability of both small and large molecules can be enhanced using permeation enhancers.

Once the solubility and permeability issues of the API have been defined, formulators should start thinking about how to increase the residence time of the API in the nasal cavity. The residence time of the drug formulation within the nasal mucosa can be increased with the use of bio-adhesive agents. Optimum viscosity needs to be selected to prevent delayed release but at the same time enhance the residence time for optimum drug absorption while not impacting spray performance or manufacturability, i.e., filling, of the drug product.

From the perspective of chemical stability, intranasal formulations can be optimized to maintain stability and potency of the drug. The stability of the API can be enhanced using stabilizers, such as chelating agents and antioxidants, in the formulation. Nasal powders confer better stability compared to liquid products. In addition, the development strategy should also ensure that the formulation is compatible with both the manufacturing equipment and, throughout the shelf-life of the drug product, the device components.

What are some key considerations when developing an intranasal product? What types of nasal drug delivery devices are there?

AMANCHA AND WILCOX: Intranasal products can be used to treat both acute and chronic indications. The common types of nasal drug delivery devices include powder devices and liquid devices. These devices are available as unit-dose or bi-dose, which are typically used for acute indications, and multi-dose delivery systems for chronic conditions. Fill volumes depend on the application with volumes up to 120 µL for unit-dose devices and up to 30 mL for a multi-dose device. For nasal powders, fill weights typically vary from 10 – 25 mg. Device selection depends mainly on the indication, and the expected dosing frequency.

For solution formulations, there are several key considerations such as API solubility/stability/permeability, which can impact potential dose, solution stability, osmolality, bioavailability, and pH or propensity to cause local irritation. The viscosity of the formulation is critical, as it affects the performance of the spray pump, influences residence time of the drug at the site of absorption and impacts device filling during manufacturing.

For powder formulations, powder flow is an important attribute when considering the small quantities of powder to be filled into each device. The physical stability of the powder is an important characteristic, as are the size, shape and surface properties of the powder particles, as these factors can all impact the redispersion or aerosolization of the powder and, as a result, the performance of the drug product.

What are some best practices in manufacture and scale-up?

AMANCHA AND WILCOX: In designing the manufacturing process for a nasal product, it is important to follow a systematic approach based on ensuring adherence to the critical quality attributes (CQAs) defined for the drug product, as these ensure its safety and efficacy. Scientific knowledge and risk assessments should be used to identify the material attributes and process parameters that will impact these CQAs development studies, which often involve Design of Experiments (DoE) to establish the criticality of the parameters identified. As the process is scaled, risk assessments, such as failure modes and effects analysis (FMEA), should be conducted to identify any high-risk attributes and implement a control strategy

to ensure that CQAs of the drug product are achieved.

In the case of liquid unit-dose and bi-dose products, the manufacturing process involves preparation of bulk drug product solution, filling of the solution into a vial, insertion of a plunger into the filled vial and final assembly of the filled vial into the nasal actuator device.

For production of the drug product solution, custom-made vessels provide control of mixing (speed and duration), pH, temperature and the vessel headspace. Filling and assembly equipment should be designed to provide accurate and precise control over the required tolerances for filling, plunger insertion and assembly operations. For preservative-free unit- and bi-dose systems, bulk product sterile filtration or terminal sterilization may be employed during manufacturing to prevent microbial contamination.

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For more information watch the webinar Intranasal Drug Delivery-Identifying Challenges and New Product Opportunities.

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Getting a Nose for Vaccines

Felicity Thomas

The intranasal route of administration is showing clinical promise, particularly for COVID-19, but there are multiple hurdles to overcome to ensure successful formulation.

The SARS-CoV-2 outbreak, which started late in 2019, has demonstrated how devastating novel infections can be for the global population. In response to the infectious threat posed by the novel coronavirus, the pharmaceutical industry rallied and managed to develop effective parenteral vaccines in record breaking speeds. However, the COVID-19 pandemic has also brought to the fore the development and distribution challenges associated with mass vaccination programs as well as difficulties ensuring equitable access to vaccines—a particular challenge for low-income countries.

Rationale behind a mucosal route

Mucosal pathogens, such as SARS-CoV-2, are a major cause of infectious diseases across the world, and the mucosal route of vaccination has been of interest for some time, primarily due to the induction of immune response that is achievable with this form of delivery (1).

GETTING A NOSE FOR VACCINES

"Spraying a solution into the nasal cavity is simple for administration purposes; however, some of the formulation may leak from the nasal cavity or into the oral cavity, which would reduce potential therapeutic effect and dose."

Although there are numerous avenues available for mucosal vaccination, the most commonly employed routes are via the mouth and nose. However, the number of licensed mucosal vaccine formulations is limited, and the available formulations tend to use attenuated strains of pathogenic bacteria or viruses, which carry specific risks such as reactogenicity and post-vaccination reversion of the pathogen to a virulent form (1).

Nevertheless, mucosal vaccines provide a strong immune response in patients, both in mucosal sites and systemic circulation (2). Additionally, these types of vaccines also offer cost and administration benefits over the traditional injectable forms (2).

Formulations for intranasal vaccines

Nasally administered vaccines are widely accepted and easily accessible, and have reportedly achieved a better systemic bioavailability and protection from gastric enzymes when compared with orally or parenterally administered vaccines (3). Yet, there are multiple hurdles that can hamper development of nasal vaccines.

Challenges to the formulation of nasal vaccines include, but are not limited to, the size of the dose required, limited efficacy of the vaccine due to mucociliary clearance, the necessity for adjuvants to enhance immunogenicity, restricted delivery volume in the nasal cavity, and normal human defense mechanisms (3). According to expert opinion, the incorporation of effective adjuvants that can trigger both mucosal and systemic immune responses are necessary for noninvasive vaccine delivery, and a more extensive understanding of mucosal immunity is required (4).

Currently, the commercially available intranasal vaccines are FluMist/Fluenz Tetra (AstraZeneca) and Nasovac (Serum Institute of India), which are both liquid, live-attenuated vaccines for influenza administered via a nasal spray (5). Other formulations for nasal vaccines include solutions administered via drops, powders, gels, and solid inserts, although there are no other nasally administered vaccines approved for marketing authorization globally.

Spraying a solution into the nasal cavity is simple for administration purposes; however, some of the formulation may leak from the nasal cavity or into the oral cavity, which would reduce potential therapeutic effect and dose. To overcome these potential issues, it has been suggested by some experts that gelling agents, such as polymers, included in

the formulation could increase the residence time of the vaccine in the nasal passage (5).

Solid formats for nasal vaccines can offer the advantage of being more stable than liquid formulations but may have disadvantages in terms of cost and ease of administration due to the potential requirement of specialist applicators. Additionally, there has been interest in the development of particulate carrier systems, such as liposomes, for vaccine products (5). To achieve success, however, vaccine formulations that are designed for intranasal administration must maintain the antigen stability, provide sufficient residence time in the nasal mucosa, and should be compatible with other components, such as adjuvants (6).

Clinical prospects for COVID-19

For COVID-19, it has been specified that the intranasal route of administration for a vaccine is promising due to the fact that the normal route of infection for the SARS-CoV-2 virus is also via the nose (6). Furthermore, it is widely reported that vaccines administered intramuscularly are less likely to provide immunity protection in the upper respiratory tract—the area of primary attack from SARS-CoV-2.

At the time of writing, the World Health Organization (WHO) has reported that there are 112 vaccines in clinical development and 184 in pre-clinical development for COVID-19 (7). Of those candidates in clinical phase, only eight vaccines are formulated for intranasal administration (7).

The furthest along the clinical lifecycle, according to WHO, are a viral vector (replicating) vaccine being developed by the University of Hong Kong, Xiamen University, and Beijing Wantai Biological Pharmacy, and a protein subunit vaccine being developed by the Center for Genetic Engineering and Biotechnology (7). Another potential intranasal candidate from Altimmune is no longer in development as a result of inadequate immune response in healthy volunteers (8).

Of the vaccines that currently have authorization from regulatory bodies to treat COVID-19, only one is in clinical development as an intranasal formulation (7). The University of Oxford announced the launch of a study investigating the efficacy of nasal administration of the ChAdOx1 nCoV-19 vaccine, which was originally co-developed for intramuscular administration with AstraZeneca, earlier in 2021 (9). The trial will assess the efficacy and immune response of either one dose or two doses of the intranasal vaccine in healthy participants and is expected to take four months (10).

Regarding the other potential intranasal COVID-19 vaccines in clinical development: two are live attenuated virus vaccines—COVI-VAC from Codagenix and Serum Institute of India, and MV-014-212 from Meissa Vaccines; two are non-replicating viral vector vaccines—BBV154 from Bharat Biotech International and PIV5-vectored vaccine from CyanVac; and one is an inactivated virus for intramuscular or intranasal administration

from Laboratorio Avi-Mex. There is an additional protein subunit vaccine listed in WHO's COVID-19 vaccine candidate tracker, which is administered intramuscularly for the first two doses and then intranasally for a third dose, from Razi Vaccine and Serum Research Institute (7).

Another potential intranasal candidate that is currently in the pre-clinical stage is a vaccine that uses a common poultry virus, the Newcastle Disease Virus, to produce spike proteins of SARS-CoV-2 (11). The collaborative effort from the University of Lancaster (United Kingdom) and the Texas Biomedical Research Institute has garnered positive results with reductions in both disease impact and transmission in animals (12).

Rokote Laboratories Finland—an academic spin-out company from the University of Eastern Finland and the University of Helsinki—has secured funding that will help it push forward with clinical development of its intranasal COVID-19 vaccine candidate, FINCoVac (13). The vaccine is based on gene transfer technology that has proven successful in other fields.

A further intranasal candidate is in development by Dutch company Intravacc (14). The SARS-CoV-2 Outer Membrane Vesicle based recombinant spike protein candidate has delivered positive pre-clinical results in mice and hamsters, and the company hopes to move forward to in-human trials quickly. And, researchers from TheraVectys—a spin-out from Institut Pasteur—have been developing a lentiviral vector vaccine candidate, which it reports would represent "a second generation vaccine that could generate a durable cellular response against the original SARS-CoV-2 strain, existing, and future variants" (15).

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Intranasal Drug Delivery: Identifying Challenges and New Product Opportunities

Jan Neelissen, Ph.D., David Wilcox, Kiran Amancha, Ph.D., and Professor Dr. Regina Scherließ

End-to-end solutions and the right equipment are necessary to support the market as intranasal drug delivery increases.

Introduction

The drug delivery market continues to evolve with ongoing exploration of novel approaches beyond conventional oral dosage forms. The intranasal delivery route has been frequently used for the local treatment of allergic rhinitis and cold symptoms. However, it is now recognized as an alternative route of systemic drug delivery for a variety of indications, such as migraine, seizures, breakthrough pain, and opioid overdose. Although there are many advantages to intranasal drug delivery, the development of nasal products is extremely complex, with additional complications arising from the relationship between the drug, delivery device and patient-related factors. As such, physicochemical properties of the drug, the device and the formulation are the critical factors that will influence a product's success. Additionally, physiological-based pharmacokinetic (PBPK)

modeling has become a very useful tool in intranasal product development as it provides an understanding of the drug's expected performance early in development.

Fundamentals of Intranasal Drug Delivery

There are several advantages to the intranasal administration of medications, including:

- Circumvention of first pass loss by the gut wall and liver
- Low drug degradation after administration
- Ease of administration
- Rapid drug absorption for quick onset of action
- A noninvasive alternative to parenteral administration
- Direct access to the brain via olfactory and trigeminal nerve, thereby avoiding the blood-brain barrier

These benefits have led to increased interest in the use of the intranasal route for drug delivery; however, there are inherent considerations and challenges associated with the development of drug products for this delivery route

These benefits have led to increased interest in the use of the intranasal route for drug delivery; however, there are inherent considerations and challenges associated with the development of drug products for this delivery route, as described below.

Considerations for Development of Intranasally Administered Products

When developing a drug product for nasal administration, there are several factors to consider, including:

- Is the drug designated for local or systemic delivery?
- Will it be for treating acute or chronic conditions?
- Are the physicochemical properties of the drug suitable for intranasal delivery?
- Can clinically relevant bioavailability be achieved?
- Can the formulation provide prolonged drug stability and ideal characteristics during and after application?
- Is the delivery device easily deployable?

There are numerous intranasal delivery devices on the market. These include single dose, bi-dose or reservoir devices (multi-dose systems), designed to account for whether the drug will be used for treating an acute condition (e.g., a single delivery) or for a chronic condition (multiple deliveries over time). Device design is key to the efficacy of the treatment, as it determines the velocity of the spray, droplet size, and the spray pattern, all of which influence deposition within the nasal passages.

Some excipients have an intense effect on nasal epithelial cells, causing irritation and leading to toxicity, especially at high concentrations. For these reasons, it is useful to refer to the Food and Drug Administration's Inactive Ingredient Database, which provides data on the type and amount of inactive ingredients that have been approved in products for a specific route of administration. In addition, there are numerous characterization tools to help assess various development aspects of the drug, formulation and delivery device [2]. Of those, PBPK modeling is a useful tool for the prediction of systemic absorption via intranasal administration. More specifically, the GastroPlus® PBPK software [3] offers an intranasal module that can be used to support product development by predicting exposure based on the formulation's physicochemical properties and key product parameters.

Formulation Development

A quality target product profile (QTPP) is imperative when developing a molecule for nasal administration, as it forms the foundation for product design. Product considerations include whether the drug will be used to treat an acute or chronic condition, the make-up and strength of the dose required, any stability and storage requirements, and whether it is intended for local or systemic delivery. The drug's physicochemical properties, such as molecular weight and ionization constant, also affect the delivery of intranasally administered sprays and powders. In particular, the rate of nasal drug absorption is inversely proportional to the molecular weight of the API, and un-ionized drugs are absorbed more rapidly. The drug's lipophilicity, or log P, is another important property for absorption, as higher log P compounds tend to have higher permeability. Solubility will determine whether a liquid or powder form is selected for product development. Low dose, high potency drugs are ideal candidates for achieving a fast onset of action [4].

Attributes of nasal powder vs. liquid spray

Properties of nasal powders and liquid sprays affect their development, storage and use. While powders offer improved stability, sprays tend to be less stable due to the aqueous instability of some molecules, and will also present challenges for poorly soluble APIs. Powders have longer nasal residence time, and their particle size can be engineered prior to device filling. In contrast, sprays have short residence time, and the droplet size is controlled by the delivery device and the viscosity of the liquid formulation. Liquid nasal sprays are the simplest, most flexible approach, featuring a large range of available low-cost devices. Powders, however, have a propensity to cause the patient irritation or discomfort and have limited device options and higher cost [5].

Liquid nasal spray formulation

There are numerous additives that help achieve the desired attributes for nasal spray formulations [6]. For example, several

options are available to enhance solubility, including co-solvents such as alcohol, polyethylene glycol, propylene glycol and glycerol. Cyclodextrins or surfactants like Tweens, Spans or bile salts may also be used for this purpose. For increasing residence time, viscosity modifiers or thixotropic agents can be used. Permeation enhancers can be used to enable faster onset of action.

Nasal powder formulation

For nasal powders, the API can be used in several formats including pure API as the powder fill, micronized powder blends, agglomerates of micronized powders, spray dried powders or spray-freeze dried powders. Direct filling of the API as a powder can face challenges with poor powder flow characteristics, poor dissolution, or inaccurate dosing. While micronized powders offer fast dissolution, rapid onset of action and improved bioavailability, they may also encounter manufacturing difficulties. Agglomerates of micronized powders may entail the API, the API plus excipients, or two APIs with excipients. Spray dried powders have been receiving much attention recently for nasal administration. This allows optimization of particle composition, size, shape and bulk density. Spray-freeze dried powders combine the advantages of spray and freeze drying. Being compatible with low water-soluble and temperature sensitive APIs, it is an often-used process for nasal vaccines.

Fillers or carriers for nasal powders may be soluble or insoluble in water. As with the liquid formulations, increased residence time is typically achieved with gelatin, starch, chitosan, or cellulose derivatives. Surfactants, bile salts, fatty acids, chelating agents and cyclodextrins are options for permeation enhancement [7].

Manufacturing and Scale-up of Bulk Drug Product

There are different types of intranasal products that can be developed both as liquid and powder formats. When developing and scaling up processes for these products, it is important to understand the process parameters and material characteristics that will affect the critical quality attributes (CQAs) of the product to ensure the efficacy and safety of the dosage forms.

When developing and scaling up processes for these products, it is important to understand the process parameters and material characteristics that will affect the critical quality attributes (CQAs) of the product to ensure the efficacy and safety of the dosage forms.

The processes for single-dose and bi-dose systems are similar for both powder and liquid forms. Both involve the manufacture

of a bulk drug product, which is then microdosed into a vial or container. The vessel is then assembled into a delivery device. There are several high-level considerations around the production process for the bulk drug products used in both liquid and powder nasal systems.

Production considerations for liquid nasal products

For liquid nasal products, the homogeneity and the chemical stability of the product solution is crucial. In addition, controlling for numerous manufacturing parameters will play key roles in achieving the product's CQAs, including:

- Environment
- pH
- Temperature
- Dissolved oxygen
- Oxygen headspace

Production considerations for powder nasal products

For powders, the production focuses on controlling particle size and maximizing yield. Spray drying is one technique employed for engineering particles for intranasal delivery. With this method, there are several parameters that must be considered to achieve proper control over the particles. The atomization step during spray drying affects the formation of the droplets to be dried, thus understanding the importance of the nozzle geometry, the properties of the feedstock solution, and the required atomization pressures is vital to achieving the correct droplet size. The drying step has its own set of considerations around the inlet gas, the flow rate of the gas, and the drying chamber temperature, to ensure that the proper evaporation of solvents occurs, and the intended physical properties of the spray dried material are achieved.

When scaling this type of process, the interdependence of process parameters must be well understood. This allows adjustments to the scale while maintaining control of critical aspects of the process, as well as enabling maximized yield.

Filling and Device Assembly

Several aspects of filling and assembly can influence the performance of the delivery device and ultimately affect patient outcomes. The filling operations for both liquid and powder unit dose/bi-dose products involve microdosing the formulated bulk product and filling it into a container. In the case of a liquid product, volumes up to 250 microliters are typically dosed into a glass vial. With a powder product, a polypropylene container is usually filled with small volumes of powder. Because the product fill is very small, control over the filling step is very important and demands very tight fill tolerances. Filling and correct assembly of the filled container into the final delivery device is critical to ensure the device's proper function.

Phase-appropriate manufacturing strategies

In early phase programs, only a small number of devices are required. Oftentimes,

laboratory filling can be employed, and the device is then assembled using manual assembly jigs.

As products progress into later development there is a need to produce larger numbers of devices. In this case, a peristaltic pump could be used for liquid filling, or for powders, a semi-automated dosator or drum filler [8]. For the assembly, hand presses enable robust and higher throughput operations.

Registration and commercial scale batches require the filling and assembly operations to be conducted on fully automated equipment. These systems call for more sophisticated engineering controls to ensure that the critical parameters are maintained at a much higher throughput rate to support the larger batch sizes. These systems will often include integrated process monitoring to verify correct fill weight, stop replacement and assembly operations.

Catalent's expertise, combined with its stringent in-process controls, regulatory support, robust analytical network and 30 years' worth of orally inhaled and nasal delivery experience, make it the ideal partner for the development of both nasal and inhalation products.

Conclusion

The intranasal route delivery has emerged as an alternative drug delivery option for a variety of indications. In addition to the typical challenges facing all drug developers, nasal systems have the added complexity of the interplay between the drug, device and patient-related factors. To develop nasal products, it is imperative to understand the anatomy and physiology of the nose as well as the impact of the formulation on deposition and absorption. For PBPK modeling, software is available to help predict whether a compound of interest will be amenable to intranasal administration for systemic affect.

Given the intricacies involved in nasal drug delivery, the choice of development partner is vital to success. Catalent offers end-to-end solutions, with the right equipment to support scale-up from pilot through commercial scale. Catalent's technical expertise is demonstrated by a proven track record of supporting the successful development and commercialization of liquid and powder nasal products, and orally inhaled drug products. Catalent's expertise, combined with its stringent in-process controls, regulatory support, robust analytical network and 30 years' worth of orally inhaled and nasal delivery experience, make it the ideal partner for the development of both nasal and inhalation products.

Watch the webinar to learn more: Intranasal Drug Delivery-Identifying Challenges and New Product Opportunities.

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