Nasal powder: A stable, rapid-onset strategy for systemic therapy

Utilizing particle engineering and novel devices to deliver shelf-stable, next-generation therapies

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Introduction

Nasal powder formulations have emerged as an alternative dosage form in nasal drug delivery, offering a range of benefits compared to traditional aqueous sprays. These formulations are characterized by their simple composition, often utilizing no preservative and minimal excipients, to facilitate the administration of larger drug doses [1]. This enhanced capacity for higher drug load combined with mucoadhesive properties directly contributes to improved diffusion and absorption across the mucosal surfaces, thereby significantly increasing bioavailability when compared to nasal liquids. Another key advantage of nasal powder formulations lies in their increased chemical stability due to reduced molecular mobility and water-facilitated degradation [2]. Unlike liquid formulations, they do not require preservatives since the solid state is less conducive to biological growth, making them more favorable to long-term storage and shipping. This stability can extend their effectiveness, as they remain potent without the need for refrigeration, eliminating cold chain requirements.

Indications for nasal delivery

Neurological disorders

Building on the advantages of nasal powders, intranasal drug delivery has provided new opportunities for the treatment of neurological disorders. It presents an effective and non-invasive method to bypass the blood-brain barrier, enabling direct delivery of therapeutic agents to the central nervous system (CNS). This approach has demonstrated promising outcomes in treating various neurological conditions, including Alzheimer's disease, depression, migraine and schizophrenia [3].

Vaccines and mucosal barriers

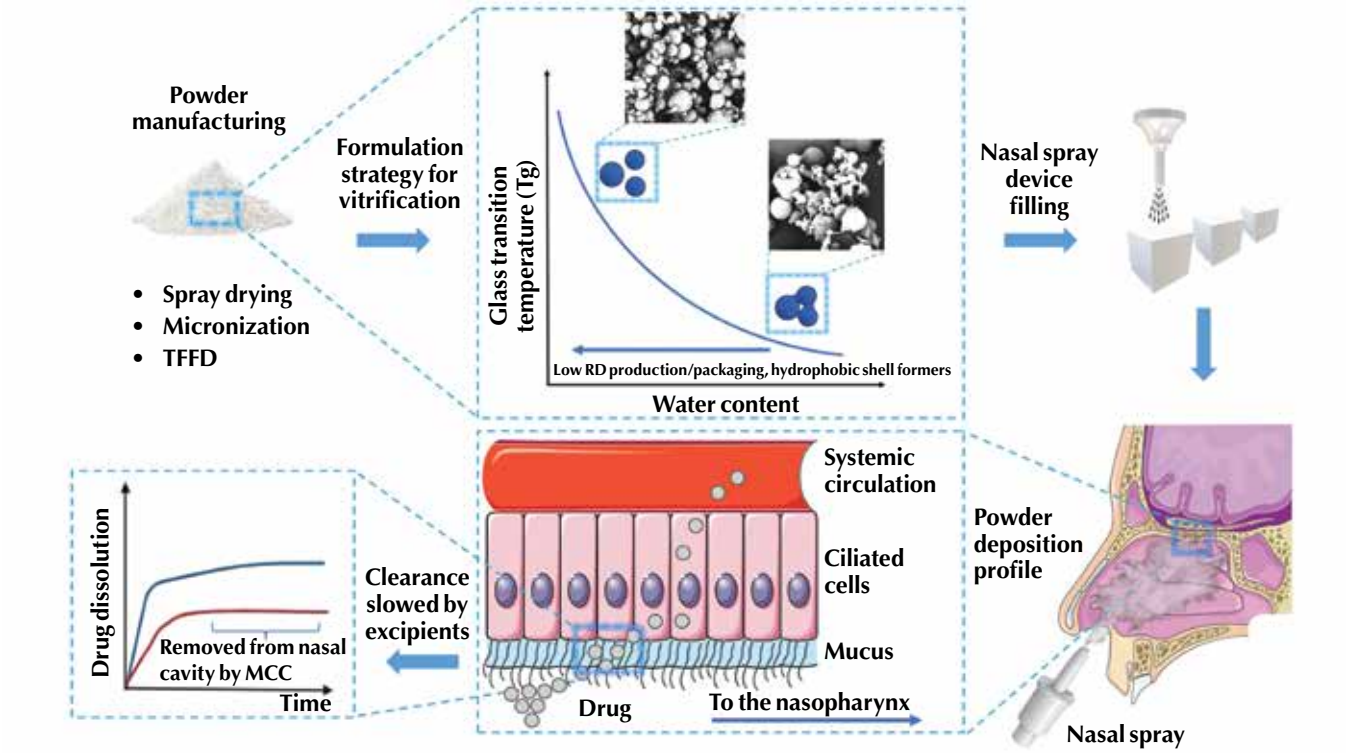
Similarly, nasal vaccines have emerged as an effective strategy in tackling respiratory infectious diseases, including COVID-19. These vaccines provide dual immunity, both at the mucosal surfaces and systemically, enhancing the body's defense mechanisms against pathogens. Although dry powder nasal vaccines are not yet commercially available [4], preclinical and clinical studies have demonstrated promising results for various antigens, including diphtheria, influenza, meningitis, anthrax, tetanus and viral gastroenteritis [5].

From a development and formulation perspective, nasal vaccines could be viewed as more straightforward compared to pulmonary vaccines. With fewer concerns for localized toxicity than pulmonary delivery [6], the nasal route may be more suitable for vaccines, adjuvants and novel excipients. Moreover, the broader particle size distribution allowances for nasal powders compared to pulmonary powders provide a wider design space during powder manufacture by spray drying, enabling the selection of less denaturing process parameters [7]. However, the development of nasal vaccines is not without challenges. One significant concern is the safety implications arising from the proximity of the nasal cavity to the CNS [8]. This necessitates careful evaluation of delivery systems to minimize potential deleterious effects on the CNS.

Another strategy to combat viral infection, which often takes hold in the upper respiratory passages before spreading throughout the body, is using

Figure 1

A schematic representation of the nasal spray drug delivery process. The process begins with manufacturing of the powder, using techniques such as spray drying, as shown at the left of the diagram. During manufacturing (top center), control over moisture and glass transition temperature (Tg) should be maintained to avoid instability such as particle fusing (as shown in the scanning electron micrographs, SEMs). After the powder is manufactured, it is filled into the spray devices. Devices are actuated into the nasal cavity (bottom right). Mucosal deposition and subsequent dissolution (bottom center and left) occur where the opportunity for absorption is limited by the rate of mucociliary clearance. Abbreviations: TFFD = thin-film freeze drying; Tg = glass transition temperature; RH = relative humidity; MCC = mucociliary clearance.



hydroxypropyl methylcellulose (HPMC) to create a physical barrier to the mucosal layer where a virus may infect and replicate. During the COVID-19 pandemic, several products composed predominantly of HPMC powder were approved in the EU and Asia [9] as medical devices (having no chemically active ingredient) for nasal administration to reduce viral infection. Once deposited in the nasal cavity, these cellulose powders swell to create an additional barrier to the mucosal surface and, when combined with appropriate buffer salts, can create a mildly acidic pH that is hostile towards many viruses [10, 11].

Emergency anaphylaxis treatment

Nasal powders are currently being explored as a potential solution to address the limitations of autoinjector-based anaphylaxis treatments, specifically around injection fears, misuse and short shelf life [12]. Recent research has demonstrated promising pharmacokinetic and pharmacodynamic results for nasal epinephrine products. These studies have found that nasal sprays can achieve pharmacokinetic results similar to traditional intramuscular epinephrine autoinjectors [13]. Specifically, the review in reference 13 indicates that the nasal sprays can achieve a median time to maximum concentration (T_{max}) ranging from 2.5 to 30 minutes—comparable to traditional epinephrine autoinjectors.

Formulation and characterization approach

Formulation considerations

The nasal mucosa is an excellent site for systemic absorption with approximately 150 cm^2 available for deposition. It is generally accepted that the nasal route will accommodate between 10 and 25 mg of powder in a single dose [14]. The formulation approach should enable these products by stabilizing the active pharmaceutical ingredient (API) and presenting it to the nasal mucosal in a way that will facilitate bioavailability and quick onset-of-action. Rapid absorption is necessary since mucociliary clearance will move mucus and deposited powder toward the nasopharynx at a rate of approximately 6 mm/min. Mucoadhesive and viscosity-enhancing polymers can be included in the powder formulation to effectively

prolong the transit time toward the nasopharynx. However, their effect should be temporary so that healthy clearance functions in the nose can resume. Figure 1 presents an overview of the approach to powder delivery to the nasal passages.

For small molecules, the manufacture of amorphous solid dispersions has been utilized extensively in oral drug delivery to enhance solubility and improve bioavailability of poorly water-soluble drugs [15]. The same approach can be utilized to create amorphous nasal powder to achieve rapid dissolution and absorption, using well-established technologies (e.g., spray drying) and nasal excipients (e.g., HPMC) approved by the United States Food and Drug Administration (FDA) [16]. For more complex biopharmaceuticals and vaccines, the preservation of the structure, conformation and encapsulation by a delivery vector is critical to consider and will be greatly affected by processing conditions, excipient selection and container closure.

Excipient selection

A limited number of excipients are utilized (approximately 60) in FDA-approved nasal products [14]. While the majority of these excipients are used in traditional liquid nasal products, some would have utility in a powder product [17]. Notable excipients for the purpose of nasal powder formulation are provided in Table 1. Ingredients used as preservatives (benzalkonium chloride), for pH/buffering (sodium hydroxide, phosphate), and tonicity (sodium chloride) are largely not useful for nasal powder formulation. However, those used as suspending agents (HPMC) and surfactants (polysorbates) do have utility. In addition to being a mucoadhesive agent, HPMC can be utilized to stabilize amorphous APIs, increasing solubility and, in turn, bioavailability. Surface active agents like polysorbates can be important tools to displace biologics/vaccines at the air-liquid interface during particle formation and drying [18].

Other ingredients have been thoroughly investigated to facilitate mucoadhesion, glass-forming stabilization and permeation enhancement. Chitosan, a biocompatible polysaccharide, is used in clinical investigations as both a nasal mucoadhesive and a permeability enhancer due to its capability to open tight junctions [19]. Utilization of chitosan during spray drying has been shown to increase feedstock viscosity (allowing for larger particles) and alter particle morphology [20]. Sugars such as trehalose, dextran and mannitol are also of great utility due to their

Table 1

Notable Excipients for Use in Dry Powder Nasal Products

Excipient		Function	Reference
In FDA-approved nasal products	Hydroxypropyl methylcellulose (HPMC)	Suspending agent, Mucoadhesion, Viscosity enhancer	14
	Beta-cyclodextrin	Bulking agent, Solubility, Absorption enhancer	33
	Dodecylphosphocholine (DPC)	Absorption enhancer	34
	Carrageenan	Mucoadhesion, Viscosity enhancer	14, 35
Commonly used in development	Chitosan	Mucoadhesion, Absorption enhancer, Adjuvant	36-38
	Alginate	Absorption enhancer	39-41
	Mannitol	Bulking agent	29, 42
	Lactose	Bulking agent	29, 42
	Trehalose	Bulking agent, Vitrifying agent	42, 43
	Dextran	Bulking agent, Vitrifying agent	44
	Cyclodextrins	Absorption enhancer	33
	Hyaluronic acid	Absorption enhancer	45
	Polyvinylpyrrolidone (PVP)	Mucoadhesion	46
	Cellulose derivatives	Mucoadhesion, Viscosity enhancer	29
	Leucine	Dispersion enhancer, Moisture protection	14

ability to hydrogen bond and vitrify large molecules, preventing alpha/beta relaxation and denaturation. The use of mannitol has been shown to replace water and reduce the local (beta) mobility of proteins, while trehalose, by forming a glassy matrix, has been demonstrated to impact global (alpha) mobility [7]. Sugars can be used independently; however, they can be used in combination due to the differing stabilizing effects they impart [21]. Residual water, which acts as a plasticizer of these spray-dried powders, will greatly affect their stability, the magnitude of which can be calculated using the Gordon-Taylor equation. Strict control over moisture levels during manufacture, packaging and shelf storage is key in ensuring the stability of engineered dry powders that are intended to be aerosolized.

Powder manufacture: Spray drying and new technologies

In the production of nasal powder, various processing methods are used [4, 22]. One such method is lyophilization, which involves freezing the liquid solution and then removing the ice by sublimation under reduced pressure. Another technique, spray freeze drying, uses a combination of atomization and quick freezing in liquid nitrogen before lyophilization. Micronized powders and micronized agglomerates have also been used to produce aerosolizable powders for nasal delivery.

More commonly, nasal powders in development utilize spray drying, which involves atomizing a liquid feedstock into a heated chamber, resulting in rapid drying of the droplets into powder. Because spray drying has become a commonly used pharmaceutical operation for oral and pulmonary powders, many have applied its use to engineer powders for nasal administration.

Spray drying is particularly well suited to engineer particles for nasal powder, where a d_{50} of 25-50 µm is desired and an amorphous API or biologic can be stabilized. The upper limit of particle size for nasal powders is not a function of deposition as in pulmonary powders (where > 5 µm is considered non-respirable), but rather limited by what size will effectively aerosolize and escape the nozzle of the selected nasal device. Conversely, the quantity of particles with a diameter of less than 10 µm should be well controlled and limited as much as possible since particles in this size range would be capable of navigating through the nasal passages and depositing in the lungs.

For stress-sensitive biologics and vaccines, careful control of outlet and collection temperatures to reduce thermal degradation is necessary. Utilization of excipients such as leucine that will compete for the air-liquid interface of the drying droplets will also reduce process stress. Further, atomization nozzles and accompanying pressures should be screened for impact on biologic/vaccine viability. Generally, higher solids concentration in feedstock will lead to more rapid particle formation, larger particles and lower proportions of material exposed to degrading forces of the air-interface [7]. Two fluid nozzles can be used at lower atomization pressures to produce larger particles suitable for nasal deposition; however, it should be noted that the generation of larger droplets can affect the ultimate dryness of the resulting powder and may require secondary drying after collection, particularly when smaller-scale spray dryers are used.

When selecting a nozzle for the production of a nasal powder, a two-fluid nozzle can be beneficial due to the smaller particle size requirements of an aerosolized powder. Understanding and control over atomization/liquid feed rates, as well as cyclone collection, are key to capturing a powder suitable for nasal delivery. A powder must be suitably small and non-cohesive so it can be readily taken up in an airstream and exit the device orifice without clogging. Another common nozzle type, pressure nozzles, (typically used for oral spray drying), have the benefit of narrow particle size distribution (PSD) and scalability, and can produce powders with particle size as small as 30 µm [15]. Pressure nozzles, however, are difficult to use at laboratory scales and tend to produce dense powders not suitable for aerosolization. [23]

While spray drying and conventional micronization continue to remain the mainstays for manufacturing respirable powders, alternative technologies are also being investigated. Thin-film freeze drying (TFFD) is a recently developed platform technology that can be applied to engineer aerosolizable nasal dry powders. Data from recent studies demonstrated the feasibility of applying TFFD to prepare dry powders of vaccines and monoclonal antibodies (mAbs) for intranasal delivery [24]. TFFD is a two-step, bottom-up method to prepare aerosolizable dry powders. Briefly, a liquid solution or dispersion, containing the APIs of interest and other excipients, is dropped onto a cryogenically cooled surface; the droplets, upon impact, spread and are rapidly frozen (100 - 1000 K/s) into thin films. Water and/or other solvents are then sublimed from the frozen films to produce dried thin films or discs. Powders prepared using the TFFD process are often highly porous, brittle and low in density, suitable for aerosolization with no or minimal additional processing.

Case study: Vaccine and mAb powder for nasal delivery using TFFD

The feasibility of applying TFFD technology to prepare dry powders of a vaccine or mAbs for intranasal delivery was recently investigated [25, 26]. Results demonstrated the successful application of TFFD in converting a complex model vaccine candidate into a mucoadhesive dry powder. The vaccine formulation,

which consisted of a protein antigen, an adjuvant carried by liposomes, and a mucoadhesive agent, exhibited desirable aerosol properties for intranasal delivery, without negatively impacting the integrity of the antigen and adjuvant after TFFD processing. According to the investigation, the TFFD vaccine powders can be effectively delivered to the desired areas in the nasal cavity, particularly in the region where nasal-associated lymphatic tissues are located, by using Aptar Pharma's Unidose powder (UDSp) nasal spray device (Aptar Pharma, Louveciennes, France). This was demonstrated by testing on 3D-printed nasal casts based on computed tomography (CT) scans of the noses of both adults and children. Figure 2 illustrates the deposition patterns of the TFFD vaccine powder in the nasal cast based on a 48-year-old adult, demonstrating that the majority of vaccine was delivered into the middle turbinate, lower turbinate and nasopharynx regions, after the powder was actuated from the device to the nasal cast. These powders, without any pre-conditioning, were manually filled into the devices. However, this does not accurately represent the handling of TFFD material in industrial settings. To enable the filling operation, the TFFD thin films would need to be transformed into flowable powders with suitable bulk properties for dosing on automated encapsulation/cartridge filling equipment.

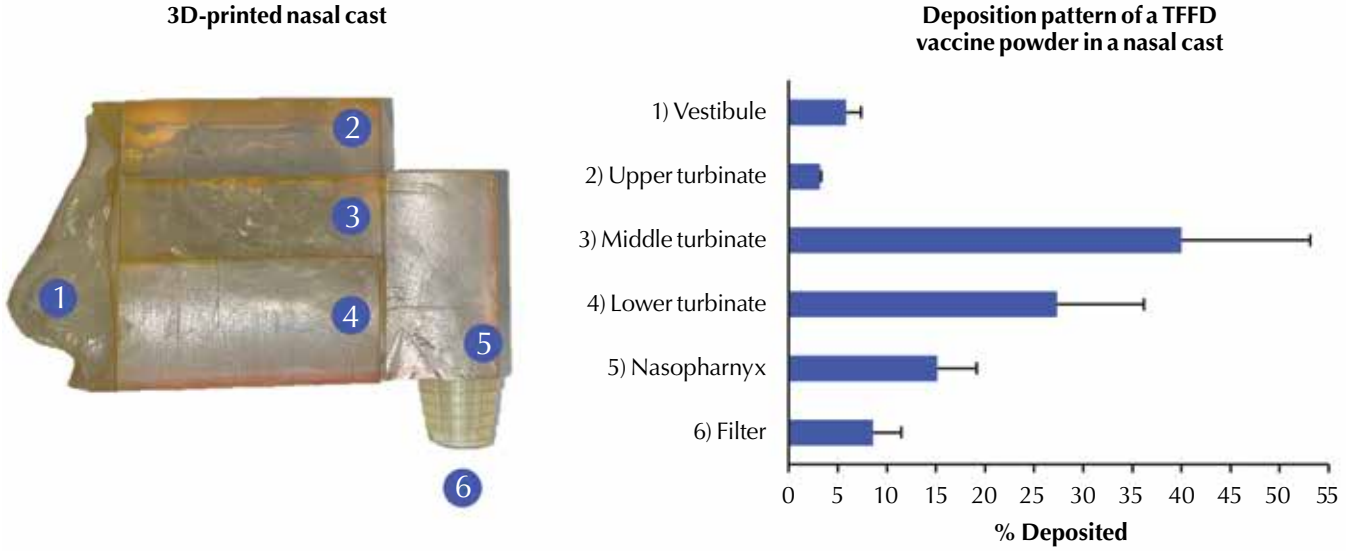
A recent study (Sandoval, Jara, Williams, Watts and Cui; unpublished data) was conducted to assess the formulation and processing strategies to improve the bulk flow and handling properties of a TFFD dry powder of mAb. Prior to thin film freezing, aqueous dispersions containing mAb formulation and excipients previously used in approved inhalation products were prepared. After lyophilization, dried thin films were milled into a flowable powder and successfully filled into Aptar UDSp nasal spray systems using drum filling technology with no significant impacts on delivered dose or particle size distribution. Due to its unique and favorable processing conditions, the TFFD technology is a promising platform for the production of a wide range of powdered nasal products, including sensitive biologics and nucleic acid-based products such as mRNA-lipid nanoparticles (LNPs).

In vitro characterization

Nasal spray powders should be characterized and tested for both physical and biopharmaceutical properties [14, 27]. The physical characteristics include particle size, morphology and residual moisture, which determine flowability, aerodynamic profiles and particle deposition patterns in the nasal cavity. Additionally, the biopharmaceutical characteristics include mucoadhesion, drug dissolution, permeation and solid-state form, which determine drug release, stability and bioavailability. *In vitro* characterization methods have been improved to assess nasal residence time and drug permeation. These methods include the use of anatomically relevant testing tools like the Alberta Idealised Nasal Inlet (AINI) (Copley Scientific, Nottingham, UK) for deposition studies, powder dissolution in physiologically relevant media to determine drug release profiles and nasal epithelial cell models for evaluating drug permeability [28]. When evaluating excipients and their effectiveness for mucoadhesion at prolonging residence time, investigators have combined a novel agar-mucin coated plate method with

Figure 2

Nasal deposition pattern of a thin-film freeze-dried (TFFD) vaccine powder in a 3D-printed nasal cast, based on the computed tomography (CT) scan of the nose of a 48-year-old male (0° coronal angle, 45° sagittal angle, 10 liters per min flow rate).



dynamic vapor sorption and rheological assessment. These tools were utilized to screen and optimize mucoadhesive excipients in a nasal powder [29]. All these methodologies can be utilized to better predict a product's clinical performance and are crucial for optimizing delivery and efficacy.

Trends and challenges in the nasal powder drug market

Market entry challenges

At present, there are only a limited number of nasal powder products available. Their indications range from treating migraine to rhinitis to diabetes. Table 2 summarizes the current nasal powder products, highlighting their indications, development stages and geographical availability.

Table 2

Representative Marketed and Developmental Nasal Powder Products (Search conducted on PharmaCircle, December 18, 2023)

Molecule Type	Active Pharmaceutical Ingredient	Indications	Phases	Country/ Region
Small Molecule	Beclomethasone dipropionate	Allergic rhinitis	Marketed	Japan
	Sumatriptan succinate	Migraine	Marketed	United States
	Dexamethasone cipecylate	Allergic rhinitis	Marketed	South Korea, Japan
	Dexamethasone cipecylate	Allergic rhinitis	Marketed	Japan
	Levodopa	Parkinson's	Phase 2	
	Olanzapine	Agitation	Phase 2	
	Dihydroergotamine mesylate	Migraine	Phase 3	United States
	Naloxone hydrochloride	Opioid dependence	Registration	United States
	Naloxone hydrochloride dihydrate	Opioid dependence	Phase 3	
Protein	Allergen, Lofarma	Allergic rhinoconjunctivitis	Marketed	Europe
	Glucagon	Diabetes, Hypoglycemia	Marketed	United States
		Diabetes, Hypoglycemia	Marketed	Europe
		Diabetes, Hypoglycemia	Marketed	Japan
		Diabetes, Hypoglycemia	Marketed	Canada
Carbohydrate	Hydroxypropyl methylcellulose	Infections	Marketed	Europe, Canada, Americas Latin
		Infections	Marketed	Asia
		Infections	Marketed	Asia, Africa
Oligonucleotide	Polyriboinosinic and Polyribocytidylic acid (a synthetic dsDNA)	Infections, Rhinovirus	Phase 2	UK
		Asthma	Phase 2	
		Infections, Influenza	Phase 2	
		Infections, Rhinovirus	Phase 2	

To overcome market entry challenges, manufacturers need to optimize powder manufacturing, have a thorough understanding of the interaction between the powder and delivery devices, and conduct a comprehensive evaluation of the local effects of powder insufflation in the nasal environment [1]. In addition, advancements that improve the effectiveness and safety of nasal drug delivery are expected to drive growth in the market for nasal drug delivery systems [30].

Commercial examples: Baqsimi® and Onzetra® Xsail®

In 2016, Onzetra Xsail (OptiNose US, Inc.) became the first nasal powder for systemic therapy to be approved for the acute treatment of migraine in adults [29]. This product is considered unique due to its breath-powered device and neat API formulation. The active ingredient in Onzetra Xsail is sumatriptan succinate, classified as a small molecule. Sumatriptan has been demonstrated effective in relieving migraine symptoms. It works by narrowing blood vessels in the brain, stopping pain signals from being sent to the brain and blocking the release of substances that cause nausea, light sensitivity and other migraine symptoms. This can make it a highly targeted and effective treatment for migraine episodes.

Baqsimi, a nasal powder formulation of glucagon, developed by Eli Lilly and now marketed by Amphastar Pharmaceuticals, is used for the treatment of severe hypoglycemia in individuals with diabetes. Approved in 2019, it was the first FDA-approved emergency treatment for hypoglycemia that could be delivered without a needle [31]. Glucagon is a hormone that raises blood sugar levels, and Baqsimi is designed to be a user-friendly, needle-free option for quickly increasing blood sugar in emergency situations. Baqsimi powder is produced by freeze drying and filled into the Aptar UDSp. The nasal powder form of glucagon can offer several advantages, including ease of administration, especially in situations where intravenous access is challenging or in cases where patients or caregivers are not comfortable with injection-based treatments. This makes Baqsimi a valuable addition to the emergency treatment options for severe hypoglycaemia.

Global regulatory trends

Global regulatory bodies, such as the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and Health Canada, are leading the way in harmonizing standards, with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) playing a significant role. While there are no universal regulations for orally inhaled or nasal medication products, the regulatory framework in these countries is well-established [32]. In the US, the regulatory process for nasal vaccines is similar to that for injectable forms. However, nasal vaccines may require additional toxicological data due to the unique risks associated with local administration in the nasal cavity, and any new excipients or adjuvants used may need additional toxicological assessment for regulatory approval [5]. Clinical trials for nasal vaccines must address the broader immune responses they produce, including T-cell activation, and any associated nasal delivery devices will be subject to standard regulatory evaluations for combination drug-device products [5]. Emerging markets such as the BRIC nations (Brazil, Russia, India and China) are increasingly adopting nasal spray medications and their regulatory agencies are considering adopting FDA-like control strategies. Advancements in technology are influencing the development of nasal medication delivery systems and medical devices, bringing new challenges in software integration, data protection and complex device components. The regulatory landscape is rapidly evolving to accommodate these technological advancements and ensure patient safety and efficacy.

Conclusions

Nasal powder formulations represent a significant stride in drug delivery innovation and take advantage of the nasal passages as a convenient, needle-free route for systemic and CNS drug delivery. The potential for simplified preservative-free compositions, increased chemical stability and enhanced capacity for higher drug loads are additional benefits offered by formulating as a dry powder. Leveraging these advantages, the applications of nasal powders extend to the treatment of a variety of non-respiratory indications such as neurological disorders, vaccine delivery and emergency anaphylaxis treatment.

Application of established production technologies, such as spray drying, allows for the design and manufacture of readily dispersible, shelf-stable powders in a scalable process. Further, spray drying can be utilized to improve bioavailability through solubility enhancement and incorporation of mucoadhesive excipients. Newer technologies such as TFFD also have demonstrated utility for nasal powder production, particularly for biopharmaceuticals sensitive to manufacturing stressors.

Despite a limited number of nasal powder products on the market, successful approval of Onzetra Xsail and Baqsimi have helped to set approval standards and can serve as regulatory precedents, reducing risk for future development efforts in this formulation space. With drug developers and approvers evolving to address the unique considerations of nasal drug delivery, the future holds promise for nasal powders as a robust and adaptable platform in the pharmaceutical landscape.

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