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Scope of Nasal Drug Delivery: Current Challenges

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Abstract: Currently the pharmaceutical scientists has exploring the possibilities of intranasal delivery as an alternative to other routes in the view of increasing number of reports related to problems associated with oral, parenteral and rectal routes for therapeutic delivery of different drugs.The present attemptwasfocused on nasal drug delivery systems fordifferent therapeutic potentials i.e. local, systemic, CNS delivery and vaccine delivery. The factors which affect the absorption of drugs or biomolecules through the nasal mucosa including biological, device-related and formulation factors are also discussed.This review may provide a complete and deep insight in relation to the nanotechnology based delivery systems for intranasal administration. A comparative study of conventional and novel delivery systems with respect to their advantages and shortcoming allows the in-depth information over the advancement of nasal delivery systems for different therapeutic purposes. The emphasis on current challenges and the possible solutions against them makes this attempt valuable for the researchers working on this platform.

Key words: Intranasal Drug Delivery · Nanoparticulate · Nasal Vaccination · Nose to Brain Targeting

INTRODUCTION

From the past few decades, much interest has been generated to the exploitation of the nasal route for systemic delivery of drugs to the specific site [1, 2]. Nasal drug delivery(NDD) conventionally has been used for treatment of local diseases such as nasal allergy, congestion and infections, respectively [3]. Besides itthe drug canbe delivered directly to the brain along the olfactory nerves [4]. Traditionally Peptide hormones (PHs) were administered by the parenteral route, like intramuscular(IM) or intravenous (IV) and subcutaneous injection (SC) [5]. But the Intranasal (IN) approach offers as an alternative route of administration for peptide hormones, like glucagon [6]. In order to improve the bioavailability of nasally administered drugs, nanoparticulate (NP) system has been explored in combination to nasal delivery [7]. NP drug delivery systems may enhance notably the transport of drugs (And vaccines) across the nasal mucosa [8]. The usage of nanoparticles for vaccine delivery provides worthy effect, by achieving satisfying immune responses [7]. The main advantages of IN delivery are avoidance of first pass metabolism, lowered systemic exposure to drug and quick onset of action [9]. The nasal mucosa has been examined as a possible route of administration to accomplish a faster and surpass level of drug absorption [10]. Kaur investigated that when the drug administered intranasally, vaccines can vitalize both local and systemic immune responses, respectively [9]. Intranasal routealong with formulationof biodegradable polymers, which are lipophilic by natureand nanometer range of particle size are capable to reach CNS at therapeutically effective dose [11]. A research established that there exists an undeviating anatomical connection between the nasal cavity and the CNS via paracellular and transcellular pathways as well as through trigeminal neurons which guides towards the development of CNS therapeutics for IN(intranasal) administration [12]. From such positive attributes, it's been sensible to appraise IN administration while developing the new therapeutics, for different possibilities (Fig. 1). The present attempt provides an overall development hierarchy of nasal administration of therapeutic along with the challenges and future possibilities.

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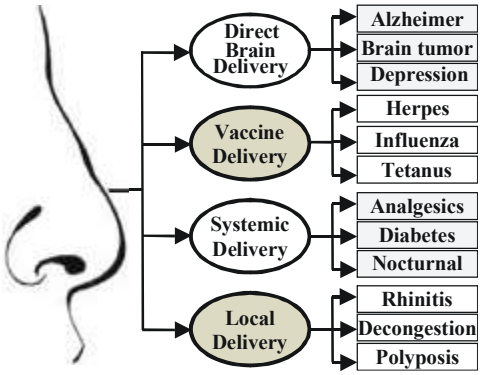

Fig. 1: Scope of nasal drug delivery[13]

Table 1: Marketed nasal products for topical/local delivery.

Product name	Drug	Indication	Manufacturer	References
Allergo-Comod	Cromolin sodium	Allergic rhinitis	Ursapharm	[16]
Lomusol®	Cromolyn sodium	Allergic rhinitis	Sanofi Aventis	[17]
Vividrin	Cromolyn sodium	Allergic rhinitis	Bausch and Lomb	[18]
Astelin®	Azelastine	Allergic rhinitis	Meda Pharm	[19]
Bactroban	Mupirocin	Eradication of nasal staphylococci	GlaxoSmithKline	[20]
Beconase	Beclomethasone dipropionate	Management of seasonal and perennial (Allergic) rhinitis	GlaxoSmithKline	[21]
Decadron*	Dexamethasone	Treatment of inflammatory nasal conditions or nasal polyposis	Merck and Co., Inc.	[22]
Flixonase	Fluticasone propionate	Management of seasonal and perennial (Allergic) rhinitis	GlaxoSmithkline	[23]
Livocab	Levocabastine	Allergic rhinitis	Janssen	[24]
Nasalcrom	Sodium cromoglicate	Management/treatment of symptoms of seasonal and perennial rhinitis	Mc Neil Consumer Healthcare	[25]
Nasivin	Oxymetazoline	Temporary relief of nasal congestion	Braco	[26]
Nasonex	Mometasone furoate	Management of seasonal and perennial (Allergic) rhinitis	Merck and Co., Inc.	[27]
Otrivin	Xylometazoline	Temporary relief of nasal congestion	Novartis	[28]
Patanase	Olapatadine	Management/treatment of symptoms of seasonal and perennial rhinitis	Alcon Laboratories, Inc.	[29]
Rhinex	Naphazoline	Decongestion	Stada	[30]
Rhinocort	Budesonide	Management of seasonal and perennial (Allergic) rhinitis	AstraZeneca	[31]
Syntaris	Flunisolide	Management of seasonal and perennial (Allergic) rhinitis	Piramal Healthcare	[32]

* Brand Discontinued in US

Nasal Route for Local/Topical Delivery: Protruding example for local/topical treatment by intranasally administered drugs are topical decongestants and topical steroids. At present it get grip of approx 2/3rd of the total market value of intranasal products [13]. As they are generally used for allergic rhinitis and as an antihistamines. IN administration is a logical delivery choice for the local/topical treatment of nasal symptoms, due to the fact that comparably low doses are efficient on topical administration with less systemic toxic effects. Factor that make an IN administration of antihistamines and corticosteroids more attractive as well as regularly preferred route of administration is that antihistamines do not cause impairment of psychomotor function or significant sedation as well. The clinical outcome of steroids is often objectionable, notably due to the poor distribution to the various regions of nose, respectively. Hence, as an effect, the nanotechnology based treatment methods for chronic sinusitis and rhinitis, have the possible market hike for the new as well as the existing topical agents, which enhanced patient compliance and bioavailability. Table 1 gives an overview of some of the marketed nasal products for local delivery [14, 15].

Nasal Route for Systemic Delivery: It seems systemic availability of drugs via intranasal administration is an effective way as compared to oral and intravascular routes [14]. A study showed an alternative routes of administration of peptide hormones as a promising approach via intranasal (IN) route for the treatment of severe hypoglycemia as itprovides the potential for rapid absorption and quick onset of action, although avoiding

hepatic first pass metabolism [7]. A new IN glucagon product AMG504-1 (Locemia Solutions, Montreal, Canada)currently being in clinical studies under the investigation process. AMG504-1 model, a glucagon delivery system consists of a dry powder glucagon formulation in compact, portable, single-use nasal powder dosing device that permits single step administration. The formulation contains glucagon along with phospholipid as absorption enhancing agent and a cyclodextrin as a bulking agent as well. Unlike insulinthat is routinely injected by the individual with diabetes, glucagon is administered by an individual who never be a trained medical professional (e.g., child, spouse, friend, work colleague, sports coach, etc.) [6].

Nasal Route for Brain Delivery: IN delivery of drugs, targeting the CNS is an area of increasing interest where a rapid and/or specific targeting is achieved, as it can circumvent the BBB and delivers the therapeutic molecules to the brain. This route has emerged as a promising approach for the delivery of drugs to the brain [33]. It explores the possibility of direct nose to brain transport of administered drugs which are difficult to pass through BBB, such as peptides, proteins and hydrophilic small molecules and improve their access to the various regionsof brain [34]. The management of condition such as Alzheimer's disease, Parkinson's disease, brain tumors, epilepsy and sleep disorders would be benefited from the development of IN delivery system, whose improved access to the brain region provides the opportunity of optimizing the efficacy of treatment, such as meningitis and stroke [35].Studies on nose-to-brain transport shows that drug reachedthe CNS after a nasal instillation mainly through three pathways, via; (i) absorption across the nasal respiratory epithelium into the systemic circulation and from there, across the BBB into the brain (Systemic pathway), (ii) direct paracellular or transcellular transport via the olfactory neurons (Olfactory neural pathway) or the olfactory epithelial cells (Olfactory epithelial pathway), or (iii) transport via the trigeminal nerves (Trigeminal pathway)[36].When drugs are administered nasally for the direct transfer from nasal crater to brain, the exact path it follows is still under an investigation [37].

Nasal Route for Vaccine Delivery: At present, IN delivery of vaccines has received some more attention and become popular area of research. It offers many distinguished advantages over parental route of administration by preventing infection with pathogens. IN immunization has reported to produce local as well as systemic immunity. Furthermore, IN vaccination does not require sterile dosing technique or a sterile product [38]. Nasal mucosa as a site of vaccine administration is extremely rich in organized Lymphatic tissues as well as in specialized cells. In humans, immune responses from nasal mucosal surface are generally simulated through interactions initiated with nasopharyngeal associated lymphoid tissues (NALT) also known as Waldeyer's ring and these organized lymphatic tissues are concerned with the first line defense against airborne microorganisms. The majority of the invading infectious pathogens gets entry into the body via mucosal surfaces and the mucosa represent the first line body defenses against infection [13]. Nasal secretions are known to contain immunoglobulins (IgA, IgG, IgM&IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa [15]. Examples of the human efficacy of intranasal vaccines include those against influenza A & B virus, proteosoma influenza, adenovirus vectored influenza, Group B meningococcal native, attenuated respiratory syncytial virus and Para influenza O3 viruses [39].

Following properties reveals the potential of vaccination method [13, 15].

- Economic, patient friendly, non-injectable and easily accessible.
- Highly vascularized.
- Availability of both mucosal and systemic immune responses.
- Doesn't require needles and syringes (a distinct advantage).
- Existence of numerous microvilli covers the nasal epithelium provides a large absorption surface area.

The nasal cavity itself stimulates the local secretory IgA as well as IgG antibodies which provides an additional first line of defense, which eliminates the pathogen before its establishment.

Nanoparticulates for Intranasal Delivery: The incorporation of drugs into the nanoparticles is a promising approach, since these colloidal formulations facilitate their transport across the mucosal barriers and protect them from the degrading milieu in the nasal cavity as well [7]. The use NP provides all sort of beneficial effects for IN delivery. The outcomes of these nanoparticulates-based systems have been intensely promising when combined with the nasal delivery. However it is not clear how this system enhance drug absorption and may cause cellular and subcellular damage

also to the biological system as well [13]. Such NP's incorporated in the form of Nanoemulsions, Nanogels, Liposomes, Carbon nanotubes, Microspheresand Quantum dots.

Nanoparticulates for Nose-To-Brain Delivery: The developed carboplatin-loaded PCL NP(Polycaprolactone Based Nanoparticles) were prepared by double emulsion solvent evaporation technique and characterized by entrapment efficiency, particle size, zeta potential, scanning electron microscopy and DSC (Differential scanning calorimetry), has improved *in vitro* anti-tumour activity as comparison to that of plain drug against human glioblastoma cells LN229 and thus for improved brain delivery, intranasal administration of carboplatin can be used, respectively [12].

The Donepezil loaded nanosuspension for direct olfactory administration was developed, which reached the brain and determined the safety profile in Sprague-Dawley rats. The developed nanosuspension was prepared by ionic cross-linking method and instilled intranasally into the nostrils of rats and drug reached into the brain via nose-to-brain pathway directly. The average size of NS was 150-200nm with a polydispersity index of 0.341 and using HPLC method its concentration was estimated in the brain homogenate. And after the study, it was anticipated that the donepezil loaded NS was capable of giving direct nose-to-brain delivery and eventually enhancing drug concentration in the brain [40].Bian *et al*., established with his work that M-C-PLA-NP is a novel brain-targeting agent for NDDS. The developed M-C-PLA-NP exhibited sustained release, smaller particle size and absolute zeta potential along with the high entrapment. M-C-PLA-NP showed its stability in the nasal cavity environment, with no significant change for 2 hrs during a period of incubation with the Lysozyme. And eventually from the in-vivo studies, it was indicated that, the M-C-PLA-NP on IN administration, not only provide a higher brain concentration of aniracetam but also lessen the spreading of the M-C-PLA-NP in other tissues as compared with the free aniracetam [41]. Jafarieh *et al.* [42] using polymeric NP (Nanoparticulate) developed and investigated the possibilities of targeting an Anti-parkinson's drug ropinirole (RH), which was loaded with chitosan NP (CSNPs), prepared by an ionic gelatin method. The RH-CSNPs were characterized for entrapment efficiency *in-vitro* release study, *in-vivo* distribution, loading capacity, particle size, polydispersity-index (PDI) and zete-potential after nasal administration for brain-targeting. The study showed, upto 18hrs sustained release profiles and eventually it concluded from the animal studies that novel formulation of RH loaded CSNPs showed superiority of nose-to-brain delivery than that delivered by RH solution with a consequent increase in bioavailability. Jain *et al.* developed and investigated artemether-loaded nanostructured lipid carriers (ARM-NLC) usingcentral composite design for IN delivery. Microemulsion method was applied in preparation of ARM-NLC with optimized formulation having zeta-potential of -34.4mV and particle size of 123.4nm, respectively. As, solid and liquid lipid materials of lipid NP, Trimyristin™ and medium chain triglycerides (MCT) were chosen. The developed formulations were non-toxic and conformed by *in-vitro* cytotoxicity assay using nasal histopathological studies and SVG p12 cell line on sheep nasal mucosa and the developed formulation showed sustained release up to 96hrs and ex-vivo diffusion study revealed that ARM-NLC had significantly lower flux as compared to ARM-SOL.Thus the brain uptake studies and pharmacokinetic in rats showed significant higher concentration of drug upon administration of NLC by IN route in the brain was maintained up to 6hrs owing to slower release of drug [43]. Zhao *et al*. [44] developed IN phospholipid-based gelatin NP encapsulating fibroblast growth factor to the target the brain. Treatment effect assessed by quantifying rational behavior, along with monoamine neurotransmitter levels. Water-in-water emulsion method, after that, freeze dried method were used in the preparation of gelatin nanostructured lipid carrier(GNLs). As comparison with the gelatin nanoparticle(GNs), GNLs possessed better profile, with the zeta potential -38.2± 1.2mv and particle size 143±1.14nm. Thus, GNLs showed obvious therapeutic effects on hemiparkinsonian rats and no adverse impact on the integrity of nasal mucosa and these are efficiently enriched exogenous bFGF in striatum and olfactory bulb respectively. Table 2 gives an overview of some of the brain targeted intranasal formulations.

Nanoparticulates for Gene Delivery: BT Harmon *et al*., showed in their work that, IN delivery of unimolecularly compacted DNA NPs (DNA nanoparticles), successfully transfect cells in the rat brain, which consists of single molecules of plasmid DNA enhanced green fluorescent protein (eGFP) which compacted with 10kDa PEG (Polyethylene glycol) substituted Lysine 30mers (Ck30PEG10k). After 2-days of pCG (Plasmid) DNA NP injection, first experiment were conducted to conform whether PCG NPs were successfully transfect cells or not along with eGFP expression in the rat brain, respectively.

Table 2: Various brain-targeted intranasal formulations

Drug	Indication	Category	Formulations	References
Amiloride	Antiepileptic	Diuretics	Nanoemulsion	[45]
Bromocriptine	Parkinson's diseases	Dopamine D2 agonist	Chitosan-loaded nanoparticles CS-BRC-NPs	[46]
Buspirone HCL	Anxiety	Anxiolytic agent	Bus-chitosan nanoparticles	[46]
Clonazepam	Status epileptics	Benzodiazepine derivative	Mucoadhesive microemulsion	[46]
Deferoxamine	Cerebral ischemia	High-affinity iron chelator	Nasal solution	[46]
Didanosine	HIV infection	HIV reverse transcriptase inhibitor	Chitosan-loaded nanoparticles	[46]
Doxorubicin	Antitumour	Anthracycline antibiotics having antitumour Activity	Niosomes	[47]
Duloxetine	Depression	Serotonin and norepinephrine reuptake inhibitor (SNRI)	Nanostructured lipid carrier (NLC)	[46]
Erythropoietin	Cerebral ischemic	Hematopoietic Growth Factor	Nasal solution	[46]
Estradiol	Alzheimer's diseases	Steroid hormone	E2-loaded chitosan nanoparticles	[46]
Hexarelin	Stimulate GH secretion	Growth hormone–releasing neuropeptide	Nasal solution	[46]
Interferon-Beta	Multiple sclerosis	Anti-inflammatory cytokines	Nasal solution	[46]
Lorazepam	Insomnia, anxiety and epilepsy	General anaesthetics slower acting drugs	Microemulsion Gel	[48]
Melatonin	Sleep disorders	Sedative-Hypnotics	Gel suspension	[49]
Methylprednisolone	Multiple sclerosis (MS)	Corticoids	Liposomes	[50]
Neurotoxin-1	Movement disorders	Analgesic peptide	Nanoparticles	[51]
Odorranalectin	Parkinson's disease	Smallest peptide with lectin-like activity	Cubosomes	[52]
			Nanoparticles	[53]
Olanzapine	Schizophrenia	Second-generation or atypical antipsychotic	Transfersomes	[54]
			Nanoparticles	[55]
Ondansetron HCl	Management of chemotherapy induced postoperative nausea and vomiting	Serotonin (5-hydroxy tryptamine) subtype (5HT3) receptor Antagonist	Nanoparticles	[56]
Risperidone	Schizophrenia	Dopamine agonist	Mucoadhesive nanoemulsion & solid lipid nanoparticles (SLNs)	[57]
Rivastigmine	Alzheimer's disease	Acetylcholinesterase (AChE) inhibitor	Chitosan-loaded nanoparticles CS-RHT-NPs	[58]
Ropinirole	Parkinson's disease	Dopamine D2 agonist	Mucoadhesive formulation	[59]
Sumatriptane	Migraine	Selective 5-HT 1D agonist	Micellar nanocarrier	[60]
Tacrine	Parkinson's disease	Anti-Parkinsonism Cholinergic activator	Nanoparticles	[61]
Tramadol HCl	Post-surgical pain, obstetric pain, cancer pain and chronic pain of mechanical and neurogesic origin	Synthetic opioid of amino cyclohexanol group	Microspheres	[62]
Valproic acid	Epilepsy, bipolar disorders, migraine and cancer	Aliphatic carboxylic acid with a broad spectrum anticonvulsant action	Nanostructured lipid carriers	[63]
Venlafaxine	Depression	Serotonin and norepinephrine reuptake inhibitor (SNRI)	Chitosan-loaded nanoparticles VLF-CS-NPs	[46]
Ziprasidone HCl	Schizophrenia	Fifth generation antipshychotic	Nanoemulsion	[64]
Zolmitriptan	Migrane	-	Micellar nanocarriers	[65]

The rats were killed 2 days after injection and by using eGFP-IHC and fluorescence microscopy eGFP expression was visualized. Throughout the rostral-caudal axis of the rat brain, eGF-positive cell were found sufficiently. And thus through this it confirmed that intranasal delivery of DNA NPs can transfect and express the encoded protein in the rat's brain and can bypass the BBB, by non-invasive approach for gene therapy of CNS disorders [66].

Nanoparticulates for Systemic Delivery: Kumar M. *et al*., developed streptomycin sulfate (STRS) loaded (STRS-SLNs) solid lipid nanoparticles for IN delivery. It is an aminoglycoside, a bactericidal antibiotic potent against bothGram +ve and Gram –ve organisms as well as Mycobacterium, respectively. By using patented nanocolloidal aqueous dispersion technique (Indian Patent Application 3093/DEL/2012), it was prepared with entrapment efficiency (54.83±2.1%) and small particle size (140.1±7.0nm). In comparison to free (F)-CSTRS, bio distribution studies using 99mTc showed 3.15 ad 11.0 times greater concentration in the brain blood of mice, upon IN administration of STRS-SLNs. Lower concentration (3.3 times) incriminate lower nephrotoxicity in kidneys, along with 4 and 12 times lower levels of drug in spleen and liver and it also specify its lesser accumulation in reticuloendothelial system organs [67]. As per literature search, PLGA-NPs (Polylactic co-glycolic acid) for RIS (Risedronate sodium) could be a drug delivery system for the prevention and treatment of osteoporosis via nasal route using NP approach, in order to reduce peripheral toxic effects. NPs of RIS were prepared by nanoprecipitation method. Table 3 gives an overview of some of the marketed nasal products for systemic delivery.

Table 3: Marketed nasal products for systemic delivery

Product name	Drug	Indication	Manufacturer	References
Aerodiol	Estradiol	Management of menopause symptoms	Servier	[68]
Atronase	Ipratropium bromide	Treatment of bronchospasm	Boehringer Ingelheim, Belg.	[69]
Imigran®	Sumatriptan	Management of migraine	GlaxoSmithKline	[70]
Miacalcic®	Calcitonin	Post-menopausal osteoporosis	Novartis Pharmaceutical Ltd.	[71]
Miacalcin®	Salmon calcitonin	Osteoporosis	Novartis Pharma	[72]
Migranal®	Dihydroergotamine mesylate	Management of migraine	Novartis Pharma	[73]
Desmospray	Desmopressin acetate	Nocturnal Enuresis	Ferring Pharmaceuticals, United Kingdom	[74]
Minrin®, Octostim®	Desmopressin acetate	Nocturnal enuresis, Management of diabetes insipidus, Hemophilia A, Von Willebrand's disease (type 1)	Ferring, Mexico	[75]
Nascobal®	Cyanocobalamine	Vit-B12 deficiency	Endo Pharmaceuticals	[76]
Nicotrol®	Nicotine	Smoking cessation	Pfizer	[77]
Stadol NS®	Butorphanol tartrate	Management of pain/Migraine	Bristol Myers Squibb	[78]
Suprecur®, Profact®, Suprefact®	Buserelin (acetate)	Prostate carcinoma, endometriosis	Sanofi-Aventis	[79]
onzetra® xsail®	Sumatriptan	Treatment of acute migraine	Avanir Pharmaceuticals, Inc.	[80]
Synarel®	Nafarelin acetate	Treatment of symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.	Pfizer Inc.	[81]
Syntocinon®	Oxytocin	Stimulates milk ejection in breast feeding mothers	Novartis Pharma	[82]
Zomig®	Zolmitriptan	Management of migraine	Cipla	[83]

Nanoparticulates for Vaccine Delivery: A suitable way is provided by the nanocarriers for the nasal delivery of antigenic molecules. The optimized vaccine nanocarriers offer a promising way for nasal mucosal vaccination. Nanoparticulate delivery systems provide more effective antigen recognition by immune cells along with improved protection and facilitated transport of the antigen, respectively [84].

Lipid-based nanocarriers and Polymeric nanocarriers are responsible for nasal antigen delivery.

ISCOMs, Liposomes, Synthetic Biomimetic Supramolecular Biovector ™and other lipid-based nanocarriers come under Lipid-based nanocarriers.

Biodegradable polyester nanoparticles, Lectin-decorated polymeric particles, Polysaccharide-based nanocarriers come under Polymeric nanocarriers, respectively.

Antigens associated with ISCOMs were efficiently processed by different antigen presenting cells (DCs, B-cells, epithelial cells, etc.) [85]. Chitosan: TPP and chitosan-PEG:TPP nanoparticles are more advantageous then the electrostatic chitosan-DNA. Complexes, as the carrier possibly provides the nucleic acids with better protection and sustained release characteristics as well [86]. Table 4 provides a list of products under investigation for IN vaccination.

Table 4: Products under investigation for IN vaccination

Vaccine/Antigen	Delivery system	References
Chlamydia Vaccine	Nanoemulsion	[87]
Pnemococcal Vaccine	C-terminal fragment of Clostridium perfringens enterotoxin (C-CPE)	[88]
Ghrelin vaccine	Nanogel	[89]
DNA vaccine (Chitosan)	Chitosan nanoparticles	[90]
Human sperm surface antigen – CD52	Liposomes	[91]
Influenza A vaccine	Nanoemulsion	[92]
Influenza subunit vaccine	N-trimethyl Chitosan nanoparticles	[93]
Influenza vaccine	PLGA nanoparticles	[94]
Foot-and-mouth disease (FMD) vaccine	Gel	[95]
Multivalent group A streptococcal vaccines	Liposomes	[96]
Ovalbumin	Liposomes	[97]
pDNA vaccine	Chitosan nanoparticles	[98]
Peptide T vaccine	PLGA microspheres	[99]

Researcher's findings in laboratory animal models and some of them being tested under clinical trial in humans are listed in Table 5.

Table 5: Marketed/Under clinical trial nasal products for vaccination

Product name/Antigen	Indication	Delivery System	Status	Manufacturer	References
Human influenza vaccine (Nasalflu Berna)	Influenza	Virosomes (Spray)	Marketed	Berna Biotech	[100]
Flu Avert®	Influenza	Drops	Marketed	Intervet/Merck	[101]
FluNsure™	Influenza	Proteosomes (Nanoparticulate)	Marketed	ID Biomedical	[13]
FluMist®	Influenza	Spray	Marketed	Astrazeneca	[102]
Maxi/Guard Nasal Vac	Bordetella bronchiseptica vaccine	Drops	Marketed	Addison Biological Laboratory	[103]
Nobivac BP®	Bordetella bronchiseptica Diseases	Suspension drops	Marketed	Intervet	[13]
Nasovac-S-(H1N1)	Swine flu	Bioadhesive delivery system	Marketed	Serum Inst. Of India Pvt. Ltd.	[104]
Calcitonin 'Novartis'100	Post-menopausal osteoporosis	Nasal spray	Marketed	Novartis Pharma	[105]
AS01™	Malaria	Liposomes	Completed	GlaxoSmithKline	[106]
AS02™	Malaria	Oil-in-water emulsion	Completed	GlaxoSmithKline	[107]
DeltaFLU	Pandemic influenza	Nasal spray	Clinical trail (Phase II)	Green Hills Biotechnology AG	[108]
Influenza (H7N9 inactivated virus)	Flu	Matrix-M1™	Clinical trail	Novavax	[109]
MEDI 534	Parainfluenza virus type 3/respiratory syncytial virus	-	Clinical trail completed	Medlmmune	[110]
MEDI 559	Respiratory Synctial Virus	-	Clinical trail (Phase I/IIa)	Medlmmune	[111]
MEDI 560	Parainfluenza virus type 3	-	Terminated	Medlmmune	[112]
Norwalk VLP	Norovirus	Powder	Phase I-II completed	Takeda Pharmaceuticals Ltd.	[113]
StrepAvax®	Group A streptococcusdiseases	Proteosomes (Nanoparticulate)	Phase II	ID Biomedical	[114]
Feline trivalent vaccine	Against calici herpes-1and parvovirus	Drops	Marketed	Heska	[115]

A good number of patents received on Nasal drug delivery formulations, even though some of them have not reached the market yet. Some of the patents related to Nasal drug delivery system are presented in Table 6.

Table 6: Patents on Intranasal Drug Delivery Systems

Drug	Indication	Delivery System	Patent	References
Benzodiazepines	Epilepsy	Nasoadhesivemicroemulsion	A Misra, TK Vyas. 1061/MUM/2004	[116]
Epinephrine	Anaphylaxis	Nasal spray	Nigel Ten Fleming US20150005356 A1 (2015)	[117]
Ketamine	Depression	Nasal sprays and inhalers	Dennis S. Charney, Sanjay J. Mathew, Husseini K. Manji, Carlos A. Zarate, John H. Krystal US20170181966 A1 (2017)	[118]
Ketorolac®	Analgesic/anti-inflammatory	Drops or spray	Giancarlo Santus, Giuseppe Bottoni, Ettore Bilato US6333044 B1 (2001)	[119]
Naloxone	Septic shock	Nasal sprays	Roger Crystal, Michael Brenner Weiss. US9211253 B2 (2015)	[120]
Proteasomes Glatiramer	Neurodegenerative disorders	Nanoemulsion	D Frenkel, Rmaron, D Burt, HL Weiner. US20060229233A1 (2006)	[121]
Noseafix®	Neuroendocrinologic disorders, such as Female Sexual Disorde (FSD)	Gel formulation	Claudia Mattern. US20170189414 A1 (2017)	[122]
Triptans, Caffeine	Migraine	Nasoadhesivemicroemulsions	A Misra, TKVyas. 1125/MUM/(2004)	[123]
Zolpidem	Insomnia	Cyclodextrin/chitosan Sols	JD Castile, YH Cheng, PG Jenkins. US0140981A1 (2007)	[124]

The Nasal drug delivery devices do exist and some are under development. Table 7 provides list of patents on Nasal drug delivery devices.

Table 7: Patents on Intranasal Drug Delivery Devices

Delivery devices	Patent	References
Pressurized Olfactory Delivery (POD) device	John D. Hoekman, Michael Hite, Alan Brunelle, Joel RELETHFORD, Rodney J. Y. HO. WO2012119153 A2. (2012)	[125]
Pfeiffer/Aptar single-dose device	Roger Crystal, Michael Brenner Weiss. US9211253 B2. (2015)	[120]
Nasal breathing device	Luigi Corsaro. US 5727543. (1998)	[126]
Nasal dilator	Martin O'Connell, Keith Yeager.US 20170027736.	[127]
Nasal inserts	Adva Beck Amon. US 8517026. (2013)	[128]
Nasal inserts	Adva Beck Arnon. 8839790. (2014)	[129]
Ergonomic nasal cannula	Darin B. Atherton. US 20170007794. (2017)	[130]
Nasal filter structure	Joseph K. Moore. US 9132300. (2015)	[131]
Nasal cavity insertion device fixture	Kenji Hioki, Hiroshi Yamada. 20140094840. (2014)	[132]

Effect of Physical Form of Delivery System

Solid: Solid drugs are chemically more stable in comparison with the solutions [133].

Powder Formulations: Powder formulations have many advantages over other formulations viz., solutions and gels, such as application in higher dosages and improved drug stability along with better drug absorption [134]. It has been shown in literature that IN delivery of Sumatriptan powder with a novel Breath Powered was more productive form of drug delivery, which provided a higher peak and rapid exposure with a lower delivered dose as comparison with speedy absorption then nasal spray [135].

Semi-Solid: For a more precise drug delivery through nasal cavity, gel approaches have been assessedin recent time [13].

Gel Formulations: Gels are more preferable then other physical form as they provide larger drug transport along with longer residence time of the formulation at the site of absorption. Gel lowers the post-nasal spread out and anterior run-off by holding the dosage form in nasal mucosa, as a result, the residence time increases and mucociliary clearance decreases [136].

An investigation suggested that nasal absorption of progesterone can be enhanced by using Carbopol nasal gel, which was done in rabbits and could be improved by using β cyclodextrin (CD) as a nasal absorption enhancer [137]. The study showed that Natesto Testosterone Nasal Gel has an advantage of self-administration with multiple dose dispenser and having a minimum incidence of local reaction [138]. The researcher's prepared (Solution, geland lyophilized powder) nasal dosage forms of metoclopramide hydrochloride (MTC) by using sodium carboxy methylcellulose (NaCMC), a mucoadhesive polymer. And it was observed that the NaCMC-based gel delivery system of MTC holds higher bioavailability than those of solution and powder [139]. Dukovski *et al*. [140] developed a nanoparticle loaded *in-situ* gelling system worthy for corticosteroid nasal delivery, responsible for the treatment of chronic rhino sinusitis with nasal polyps. They proposed lipid/alginate nanoparticle, whose size ranges from 252.3±2.4 nm, polydispersity index 0.241, with zeta-potential -31.7±1.0 mv and dexamethasone (Dex) content of 255±7 μg ml respectively, which eventually dispersed in a pectin solution of 5mg ml^{-1} that gone through a sol-gel phase transition which were triggered by Ca^{2+} available in nasal mucosa and allow delivery of corticosteroid beyond the nasal valve. The proposed study gave an *in vitro* proof-of-concept of developed system that ensure efficient corticosteroid delivery with prolonged local action due to prolonged contact time with nasal mucosa upon gelation [140].

Liquid: Liquid (suspension and solution) sprays more convenient over powder sprays for the reason that the powdersprays simply provoked the nasal mucosal irritation [141]. The nasal drug solutions are administered as nasal drops, sprays and as metered dose nebulizer. An active ingredient's dose administered depends upon the concentration of drug in the formulation and the volume of drug, respectively.

Sprays: The case study provided a guideline to quality by design (QbD) approach for suspension type nasal spray products development e.g. beclomethasone nasal spray suspension, ciclesonide nasal spray suspension, fluticasone nasal spray suspension and mometasone nasal spray suspension. This novel model can surpass generic nasal spray developments by reducing cost, development time and manpower and thus reducing number of experiments required to procure *in vitro* equivalency with innovator drug products as well [142].

Drops: Study showed that drops administered in the right manner should reach the middle meatus in greater quantities and also improved penetration of nasal valve [143].

Table 8: Challenges related to nasal drug delivery

Challenges	Resolution to the challenges
Less retention time	Increase viscosity/bioadhesive systems
Permeability of drug	Optimum drug concentration, decrease MCC
Irritation and irreversible damage of the cilia on nasal mucosa	Formulation's should be at nasal pH
Disrupt and sometimes dissolvation of nasal membrane	High concentration of absorption enhancers should be reduced
Adversely affected by pathological conditions(cold and cough)	Simultaneous use of compatible decongestants along with other therapeutic drugs.
Solubility of hydrophilic drug	Incorporation of solubilizer

Advancements in Nasal Delivery: Dr Djupesland (Opti Nose AS, Norway) came with a new concept for targeting the nasal cavity, with the device known as (OptiMist), consists of two nozzels to be inserted into a nostril. The major advantage of the device is that it minimizes the lung deposition i.e., <1% of the total dose gets collected in the lungs after bidirectional delivery and maximizes the distribution of aerosolized droplets in the nose [144]. The novel concept of Breath powered Bi Directional™ has been came into existence that responsible to overcome many of the inherent limitations of traditional nasal devices [145]. Impel NeuroPharma's Pressurized Olfactory Delivery (POD) device is an example of clinical evaluation, responsible for successful delivery of aerosolized drugs to the nasal cavity [33].

Challenges in Nasal Delivery: The transnasal delivery getting explored now a days with great interest for delivering the non-peptide small and macromolecules and neuropeptides bypassing the BBB, prevent local toxicities and achieve rapid, improved and prolonged drug delivery [146]. One of the limiting factors in nasal drug delivery, is the restricted volume of the nasal cavity, which hindered the amount of formulation that can be administered [147] while other challenges with their resolution are listed in Table 8. Without an absorption modifier, nasal administration of peptides (Such as calcitonin and insulin) and proteins results in factor called low bioavailability across the nasal mucosa, possibly owed to enzymatic degradation of the molecule during passage through the epithelial barrier and/or mucociliary elimination from the nasal cavity [15, 147]. Particle size of the droplet or powder responsible for dugs deposition, the ideal size for the retention in the nasal cavity is between 5-7 µm. It would be exhaled if particle size is <0.5 µm whereas if particle size is <10 µm, then it would be deposited in the upper respiratory tract [148]. At present, very limited adjuvants are being used in marketed vaccines, the most probable reason behind this is that, for vaccine approval, clinical trial is necessary, which are often very lengthy and difficult. Ideally, an adjuvant must be capable to stimulate cellular, mucosal and humoral immune responses discretely or concurrently, depending on the desired treatment [149]. In recent times, treatment of neurological diseases has become one of the most remarkablechallenge and in response to this challenge, nanotechnology provided promising solutions to the same.

There is a need to address some questions in order to meet the possible opportunities for the success of IN route deliver, like- it is unknown if there is a any size limit which governing what can be delivered to the brain via the intranasal route [150]. Study with dextrans suggested that there was an inverse relationship between CSF and the MW concentration following IN administration [151]. Generally, solution cannot stay for a longer period of time into the nasal cavity which leads to less retention time due to mucocilliary clearance is another major challenge for delivered a drug into a nasal cavity.Repeated uses of nasal drops cause loss of ciliary layer, loss of epithelial cell and shrinkage of mucosal layer that might be incurred by inactive or incompatible active ingredient of formulations, respectively [152]. Use of Gelling agents results in the increase in retention time of the drug along with decrease in drainage [153]. The drugs can be absorbed efficiently and quickly across the nasal membrane, when it is lipophilic and having a MW of less then 1kDa and thus polar drugs not easily transport across nasal membrane [14]. Drug's permeation can be affected by the pH of the formulation, as well as that of nasal surfaces. pH of the nasal formulation should be adjusted to 4.5-6.5 to avoid nasal irritation. In addition, prevents the growth of bacteria along with efficient drug permeation. Also permeationof the compound normally increases through nasal mucosa on increasing lipophilicity [153]. Nasal absorption and aqueous solubility of the insoluble compounds of the drug increase by the use of solubilizer. Specialized systems such as lipid emulsion [154] microspheres (Using carbopol, chitosan, 934P and lactose), films, liposomes, niosomes, proliposomes, provides a better chance of permeation for the drugs. In the perspective of sound researchers, the nasal drug delivery in combination with nano-technology undo the future understanding and therapeutics of brain function and CNS diseases.

CONCLUSIONS

The advantages of nasal administration put this cavity as a distinguish option for future drug delivery. The permeability of nasal mucosal surface offers the bioavailability comparable to systemic routes for some drugs that fact can be utilized for the development of non-invasive option of such parenteral therapeutics. The possibility of direct nose-to-brain transfer of nasally administered therapeutics also opensthe opportunitiesfor the development of new formulations for better or equivalent bioavailability with lower doses by minimizing the pre-systemic and systemic losses. Despite of number of researches reported for nasal delivery of various molecules for different purposes i.e. local, systemic, nose-to-brain and vaccine delivery, the scientific community is still lacking to utilize the maximum therapeutic benefits. The challenges associated with nasal deliverance and lack of knowledge about the mechanism responsible for disposition of nasally administered drug, restricted the development of new dosage forms for different pathological conditions especially in case of nose-to-brain transport.

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