Drug Delivery

http://informahealthcare.com/drd
ISSN: 1071-7544 (print), 1521-0464 (electronic)

Drug Deliv, 2016; 23(3): 671–683
 DOI: 10.3109/10717544.2014.920431

informa
healthcare

REVIEW ARTICLE

Nasal-nanotechnology: revolution for efficient therapeutics delivery

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Abstract

Context: In recent years, nanotechnology-based delivery systems have gained interest to overcome the problems of restricted absorption of therapeutic agents from the nasal cavity, depending upon the physicochemical properties of the drug and physiological properties of the human nose.

Objective: The well-tolerated and non-invasive nasal drug delivery when combined with the nanotechnology-based novel formulations and carriers, opens the way for the effective systemic and brain targeting delivery of various therapeutic agents. To accomplish competent drug delivery, it is imperative to recognize the interactions among the nanomaterials and the nasal biological environment, targeting cell-surface receptors, drug release, multiple drug administration, stability of therapeutic agents and molecular mechanisms of cell signaling involved in patho-biology of the disease under consideration.

Methods: Quite a few systems have been successfully formulated using nanomaterials for intranasal (IN) delivery. Carbon nanotubes (CNTs), chitosan, polylactic-co-glycolic acid (PLGA) and PLGA-based nanosystems have also been studied *in vitro* and *in vivo* for the delivery of several therapeutic agents which shown promising concentrations in the brain after nasal administration.

Results and conclusion: The use of nanomaterials including peptide-based nanotubes and nanogels (NGs) for vaccine delivery via nasal route is a new approach to control the disease progression. In this review, the recent developments in nanotechnology utilized for nasal drug delivery have been discussed.

Keywords

Intranasal, nano-delivery systems, nasal vaccination, non-invasive, nose-to-brain delivery

History

Received 1 April 2014
Revised 29 April 2014
Accepted 29 April 2014

Introduction

The present worth of the nasal product consumption in market is around US$10 billion; with a projected 10–15% annual escalation and 16 of the 20 major pharmaceutical companies have active nasal drug delivery programmes (Pires et al., 2009; Illum, 2012). Nasal delivery has conventionally been restricted to topically/locally acting therapeutic agents applied to deal with the nasal problems like common cold and nasal hypersensitivity. In recent times, however, there has been increased attention for nasal route as a substitute to oral and parenteral routes for various systemic therapeutic agents and vaccines. The highly vascularized and immunogenic nasal mucosa put frontward impending advantages in expressions of fast onset of action, enhanced bioavailability and patient compliance in parallel with superior immune response in favor of vaccines (Illum & Balle, 1978; Illum & Davis, 1991; Hinchcliffe & Illum, 1999; Lipworth & Jackson, 2000; Illum & Davis, 2001; Illum, 2002; McNeela et al., 2004; Read et al., 2005; Merkus & de Jongste, 2006; Charlton et al., 2007). Nasal delivery of therapeutics offers a cost effective and patient agreeable alternative to parenteral routes. A drug delivered via nasal route gives response promptly in comparison to oral tablets and mixtures, and the response time for therapeutic action is analogous to intravenous injection (Duchateau et al., 1986a; Schipper et al., 1994; Marttin et al., 1997; Duquesnoy et al., 1998; van Asselt et al., 1998; van der Kuy et al., 1999; Lipworth & Jackson, 2000;). The IN vaccination put forward added local immune protection for several vaccines (Bacon et al., 2000; McNeela et al., 2000; Illum & Davis, 2001; Illum et al., 2001). The human nose is a striking route for the delivery of therapeutics making an allowance for various existing substances, as well as the multifarious protein drugs being evolved as a result of biotechnological researches by companies (Illum, 1991; Marttin et al., 1998; Davis & Illum, 2003). Advancement in nasal formulation expertise and innovative delivery technologies such as nanotechnology may perhaps offer indispensable advantages and spread out the medicine market for nasal delivery of drugs and vaccines (Douglas et al., 1987; Critchley et al., 1994; He et al., 1999; Brooking et al., 2001; Illum, 2007; Mistry et al., 2009b; Illum, 2012).

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Countenance with rising drug development expenditures and violent generic rivalry, pharmaceutical business are under mounting anxiety to uncover ways to augment and stretch out the profitability of both existing and new products along with superior bioavailability. Several of the sophisticated molecules for therapeutic use have need of more proficient deliverance than that obtainable by conventional routes and delivery systems. The dilemma of optimizing the bioavailability and patient compliance of these precious molecules are additional considerable drivers for the development of novel drug delivery systems. If successful, nasal delivery associated with nanotechnology-based novel delivery systems offer dominant utensils for improving effectiveness and distinguishing a product from other contenders. In addition, more efficient and patient agreeable delivery systems and dosage forms can get longer patent periods and raise competitiveness. On the whole, this offers pharmaceutical industries the standpoint to sustain and raise their market share for only a reasonably restricted investment.

Rationale for commencing nasal delivery of therapeutics

The nasal administration of drugs for systemic outcome has been extensively investigated and efforts have been accomplished to transport a huge number of compounds, counting peptides and proteins for various diseases, by this route (Table 1; Slot et al., 1997; Hinchcliffe & Illum, 1999; Lipworth & Jackson, 2000). The user-friendliness of the nasal route makes self-medication possible in consequence improving patient compliance in comparison to parenteral routes (Duquesnoy et al., 1998; Illum, 2003). The nasal cavity has a comparatively large absorptive surface area and the high vascularity of the nasal mucosa makes sure that absorbed compounds are promptly distributed. Drugs absorbed into the affluent network of blood vessels get ahead directly into the systemic circulation in this manner circumventing hepatogastrointestinal first pass metabolism (Chandler et al., 1994; Illum, 2002; Costantino et al., 2007). The plasma pharmacokinetic profile after IN drug absorption for several drugs is comparable to that achieved with intravenous bolus injection (Duchateau et al., 1986a; Illum et al., 2002). Nasal drug therapy is supposed to potentially permit a better patient control of blood concentrations levels of drug and by doing so avoid numerous chronic complications associated with diseases (van Asselt et al., 1998; He et al., 1999; van der Kuy et al., 1999). Even though nasal drug delivery would not be unanimously appropriate, it is envisioned that nasal therapy could be an adjunct to parenteral therapy in various diseases.

Table 1. Investigational target diseases/pathological conditions for nasal delivery.

Diseases/pathological conditions	
• Allergic rhinitis	• Motion sickness
• Alzheimer's diseases	• Nasal polyposis
• Cancer	• Nocturnal Enuresis
• Decongestion of nasal cavity	• Osteoporosis
• Depression	• Pain management
• Diabetes mellitus	• Parkinson's diseases
• Hormones deficiency	• Smoking cessation
• Local nasal infections	• Vaccination against various diseases
• Migraine	• Vitamins deficiency

Notwithstanding the potential of the nasal route (Figure 1), there are numerals of aspects which limit the absorption of peptide and protein drugs from nasal mucosa for systemic delivery. As a result, the bioavailability of peptide and protein drugs achieved subsequent to IN administration tends to be inefficiently low compared to parenteral routes. This is being a sign of the fact that only a few IN peptide and protein preparations are presently available for systemic medication. In the absence of absorption enhancers, IN absorption of peptide and protein drugs is insignificant (Deurloo et al., 1989; Illum, 1991; Marttin et al., 1998; Davis & Illum, 2003). The typical physiology of the human nose presents a number of barriers to peptide and protein drug absorption. These barriers take account of the physical exclusion from the site of deposition in the nasal cavity by the mucociliary clearance possessions, enzymatic deprivation in the mucus deposit and nasal epithelium and the low permeability of the nasal epithelium (Arora et al., 2002; Ozsoy et al., 2009; Bahadur & Pathak, 2012b; Pisal et al., 2012). Recognition of prospective of the nasal path for peptide and protein deliverance or in fact the deliverance of other ''challenging'' molecules necessitates an understanding of the structure, composition and function of the nasal cavity, the barriers for nasal delivery which limit their absorption and the approaches by which these barriers may possibly be triumph over.

Nasal route for topical/local delivery

Topical decongestants and topical steroids at present get hold of more than two thirds of the total market value of nasal products (Table 2). Allergic reactions are rising globally and influence 5–10% of the population (Bitter et al., 2011; Illum, 2012). Topical steroids correspond to the drugs of preference for patients with chronic allergic and non-allergic mucosal inflammation. In addition, the topical steroids used in treatment of patients suffering from rhinitis and sinusitis. Persistent rhino-sinusitis and nasal polyposis are often allied

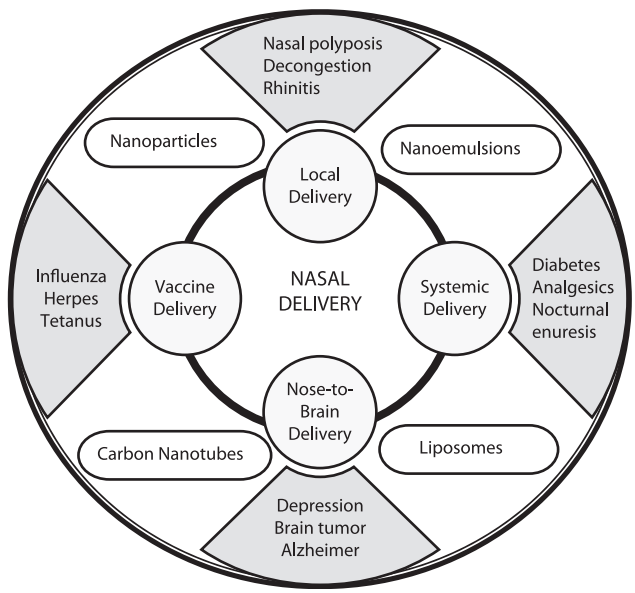

Figure 1. Potential of nasal delivery.

Table 2. Marketed nasal products for topical/local delivery.

Product name	Drug	Indication
Allergocrom®, Vividrin®, Lomusol®	Cromolyn sodium	Allergic rhinitis
Astelin®, Allergodil®	Azelastine	Allergic rhinitis
Bactroban®	Mupirocin	Eradication of nasal staphylococci
Beconase®,Vancenase®	Beclomethasone dipropionate	Management of seasonal and perennial (allergic) rhinitis
Bisolnasal®	Tramazoline	Decongestion
Decadron®	Dexamethasone	Treatment of inflammatory nasal conditions or nasal polyposis
Flixonase®	Fluticasone propionate	Management of seasonal and perennial (allergic) rhinitis
Livocab®, Livostin®	Levocabastine	Allergic rhinitis
Nasacort®	Triamcinolone acetonide	Management of seasonal and perennial (allergic) rhinitis
Nasalcrom®	Sodium cromoglicate	Management/treatment of symptoms of seasonal and perennial rhinitis
Nasivin®	Oxymetazoline	Temporary relief of nasal congestion
Nasonex®	Mometasone furoate	Management of seasonal and perennial (allergic) rhinitis
Otrivin®	Xylometazoline	Temporary relief of nasal congestion
Patanase®	Olapatadine	Management/treatment of symptoms of seasonal and perennial rhinitis
Rhinex®	Naphazoline	Decongestion
Rhinocort®	Budesonide	Management of seasonal and perennial (allergic) rhinitis
Sinex®	Phenylephrine	Temporary relief of nasal congestion
Syntaris®	Flunisolide	Management of seasonal and perennial (allergic) rhinitis

Table 3. Marketed nasal products for systemic delivery.

Product name	Drug	Indication
Aerodiol®	Estradiol	Management of menopause symptoms
Atronase®	Ipratropium bromide	Treatment of bronchospasm
Imigran®	Sumatriptan	Management of migraine
Instany®	Fentanyl	Pain management
Miacalcic®	Calcitonin	Post-menopausal osteoporosis
Miacalcin®	Salmon calcitonin	Osteoporosis
Migranal®	Dihydroergotamine mesylate	Management of migraine
Minirin®, Desmospray®	Desmopressin acetate	Nocturnal Enuresis
Minrin®, Octostim®	Desmopressin acetate	Nocturnal enuresis, Management of diabetes insipidus, Hemophilia A, von Willebrand's disease (type 1)
Nascobal®	Cyanocobalamine	Vit-B_{12} deficiency
Nicotrol®	Nicotine	Smoking cessation
Stadol NS®	Butorphanol tartrate	Management of pain/Migraine
Suprecur®, Profact®, Suprefact®	Buserelin (acetate)	Prostate carcinoma, endometriosis
Synarel®	Nafarelin acetate	Treatment of symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.
Syntocinon®	Oxytocin	Stimulates milk ejection in breast feeding mothers
Zomig®	Zolmitriptan	Management of migraine

with asthma and need lifelong treatment. On the other hand, the clinical outcome of topical steroids is often unacceptable, principally due to the poor distribution to the nose and sinuses (Illum & Balle, 1978; Balle et al., 1979; Duchateau et al., 1986b; Merkus et al., 1999b; Lipworth & Jackson, 2000; Merkus & de Jongste, 2006; Kantar, 2010). As a consequence, superior nanotechnology-based treatment methods for chronic rhinitis and chronic sinusitis have the prospective for ample market growth for existing and new topical agents and unlock fresh opportunities for novel nasal delivery systems proficient to enhance patient compliance and bioavailability.

Nasal route for systemic delivery

For exerting its primary rationale as a filter and air-conditioner shielding the subordinate airways, the human nose has a complex arrangement lined by extremely vascularized mucosa (Jones, 2001; Illum, 2006). The uncomplicated access to this large vascularized facade makes the nasal route predominantly remarkable for absorption of therapeutic agents which are complicated to deliver with conventional routes and usually necessitate injection. Rapid absorption and the prompt onset of action are crucial in the management of intense, acute pain and in managing severe pathological conditions like cardiovascular attacks, seizures, hypoglycemia, nausea and vomiting. Nasal deliverance evades the problems allied with degradation of drugs in the stomach and in the liver, which put forward it predominantly suitable for several of the latest recombinant peptide and protein drugs (Pires et al., 2009; Malerba et al., 2011; Bijani et al., 2012; Chung et al., 2012). The nasal delivery presents a smart needle-free substitute which may possibly improve patient compliance and permit unmitigated exercise of self-medication for many persistent diseases (Jones et al., 1997; Chung et al., 2012). This is the reason that systemically acting drugs such as calcitonin for the treatment of osteoporosis, cardiovascular drugs such as desmopressin, NSAIDs and anti-migraine drugs are already marketed as nasal formulations (Table 3) and many more are in the pipeline.

Nasal route for brain delivery

Systemic treatment of many central nervous system (CNS) diseases, such as depression, epilepsy, schizophrenia,

migraine etc. is considerably impaired by limited delivery of therapeutic agents. Deprived CNS access is principally associated with discriminating barricades that seize the CNS from the circulatory system. This barrier is breached by the exploitation of nanotechnology-based nasal delivery systems through olfactory region. The olfactory section to be found in the upper distant divisions of the nasal channels intimates the prospective for certain drug molecules to circumvent the blood brain barrier and penetrate into the brain (Bahadur & Pathak, 2012b). Even though the clinical potential of this drug administration route still remains controversial, there is substantial curiosity in investigating nasal route for the treatment of many intra-cerebral diseases such as Parkinson's and Alzheimer's (Merkus et al., 2003; Illum, 2004; Merkus & van den Berg, 2007; Malerba et al., 2011; Rajadhyaksha et al., 2011). Peptides and proteins are capable to penetrate into brain passing through the olfactory bulb and trigeminal pathways subsequent to nasal delivery, as an outcome escaping the blood brain barrier (Veronesi et al., 2011; Caban et al., 2012). In the opinion of sound researchers, the nasal route in combination with nanotechnology-based systems for drug delivery unbolt positive horizons for future understanding of brain function and future therapeutics of CNS diseases (Table 4).

Even though it is not easy to manage the drug penetration into cerebrospinal fluid, nasal delivery of drugs offers a lead on conventional delivery methods in view of the fact that numerous drug molecules have conformational resemblance with hormones, due to which substantial hormonal side effects arises when reached to systemic circulation. By means of nasal delivery, the extent of drug entering the systemic circulation can be markedly reduced by taking the advantage of olfactory region of nose for targeting the drug to the brain.

Table 4. Drugs and nanotechnology-based systems under investigation for nose-to-brain delivery.

Drug	Delivery system	References
Amiloride	Nanoemulsion	Jain et al. (2011)
Didanosine	Nanoparticles	Al-Ghananeem et al. (2010)
Doxorubicin	Niosomes	Bragagni et al. (2012)
Lidocaine HCl	Nanogel	Hu et al. (2009)
Lorazepam	Microparticles	Jug & Becirevic-Lacan (2008)
Melatonin	Gel suspension	Jayachandra et al. (2011)
Methylprednisolone	Liposomes	Gaillard et al. (2012)
Neurotoxin-1	Nanoparticles	Ruan et al. (2011)
Odorranalectin	Cubosomes	Wu et al. (2012)
	Nanoparticles	Wen et al. (2011)
Olanzapine	Transfersomes	Salama et al. (2012)
	Nanoparticles	Seju et al. (2011)
Ondansetron HCl	Nanoparticles	Joshi et al. (2012)
Risperidone	Nanoemulsion	Kumar et al. (2008)
	Nanoparticles	Patel et al. (2011)
Rivastigmine	Nanoemulsion	Yang et al. (2012)
	Nanoparticles	Fazil et al. (2012)
Sumatriptan	Micellar nanocarriers	Jain et al. (2010a)
Tacrine	Nanoparticles	Luppi et al. (2011)
Tramadol HCl	Microspheres	Belgamwar et al. (2011)
Valproic acid	Nanostructured lipid carriers	Eskandari et al. (2011)
Ziprasidone HCl	Nanoemulsion	Bahadur & Pathak (2012a)
Zolmitriptan	Micellar nanocarriers	Jain et al. (2010b)

The marketed nasal products containing CNS agents have a possibility of direct transportation to the brain and cerebrospinal fluid (CSF). In the view of this fact, the combination of systemic absorption and direct transfer to CNS via olfactory region or trigeminal nerves is the reason for enhanced bioavailability of CNS agents after nasal delivery. The various possibilities of drug absorption after nasal administration are shown in Figure 2. The exact mechanism for the direct transfer of drugs from nasal crater to brain is still under investigation.

When a drug administered through nasal route it may enter into the blood of general circulation, may permeate the brain directly or in some cases may follow both pathways (Illum, 2000). In general, there are three routes for the transport of drug from the nasal cavity. These routes include:

(a) entry into the systemic circulation directly from the nasal mucosa,
(b) entry into the olfactory bulb via axonal transport along the neurons, and
(c) direct entry into the brain via trigeminal nerves.

Nasal route for vaccine delivery

The nasal mucosa is the primary site of contact with inhaled antigens. The recent researches reveals the facts for understanding the working of nasal mucosal immune system, pooled with advanced molecular biology and genetic engineering, have unwrap new possibilities for the development of a novel cohort of vaccines that be able to administered via nasal route (Eyles et al., 1998b; Scheerlinck et al., 2006; Smith et al., 2012). Experimental findings in laboratory animal models have revealed that these new nasal vaccines can certainly aggravate protective immune responses, and several of them are being tested in humans under clinical trials already (Table 5; Eyles et al., 1998a; Iqbal et al., 2003; Amidi et al., 2007; Brave et al., 2008). Perhaps the key challenge for vaccine development lies in the deliverance of antigens for the stimulation of optimal protective immune reactions. The efficiency of these new advancements in vaccine development is under observation for the deliverance of new, safe, affordable and more efficient vaccines for the control of infectious disease.

In addition, mucosal surface of nasal cavity is remarkably affluent of specialized units NALT (Nasal Associated Lymphoid Tissue also known as Waldeyer's ring in

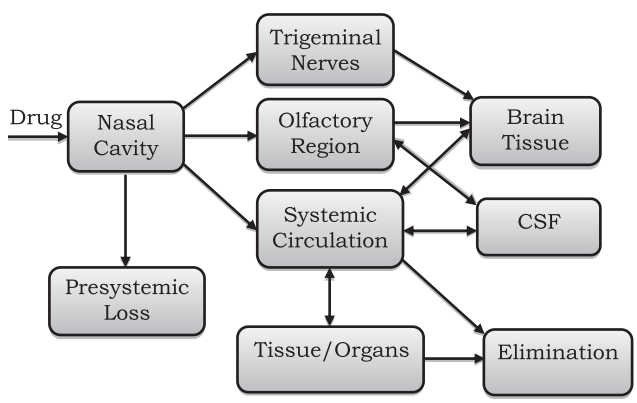

Figure 2. Possible fate of drug after nasal administration.

humans) and accommodate prearranged lymphatic tissues concerned with the first line safeguard in antagonism to airborne infectious diseases (Illum, 2012; Vujanic et al., 2012). Nasal vaccination evades the soreness and inconvenience allied by means of injection, and stimulates local mucosal defense as sound as a systemic immune reaction. Furthermore, nasal vaccination provokes defense in distant mucosal organs and come forward to offer broader safeguard than injected vaccines. A number of nasal vaccines are in the pipeline and anticipated to approach the market in the near future (Wang et al., 2012a,b).

Conclusively, following properties presents nasal delivery as a potential vaccination method:

- economic, patient friendly and easily accessible;
- extremely vascularized;
- existence of abundant microvilli wrapping the nasal epithelium assembles a large absorption surface area;
- subsequent to vaccination by nasal route, both mucosal and systemic immune reactions are provoked;
- immune reaction can be stimulated at remote mucosal spots due to the propagation of effector immune units in the general mucosal immune synchronization;
- be capable to exploit for the vaccination of bulky population cohorts; and
- does not involve needles and syringes, which are feasible resources of infectivity.

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

Product name	Indication	Status
Feline trivalent vaccine against calici herpes-1 and parvovirus	Herpes	Marketed
Flu Avert®	Influenza	Marketed
FluINsuru®	Influenza	Phase 2
FluMist®	Influenza	Marketed
Human influenza vaccine	Influenza	Phase 1/2
Maxi/Guard Nasal Vac®	Bordetella bronchiseptica diseases	Marketed
Nasalflu Berna®	Influenza	Marketed (withdrawn)
Nobivac BP®	Bordetella bronchiseptica diseases	Marketed
StrepAvax®	Group A Streptococcus diseases	Phase 2

To develop the safer and better vaccines, a lot of efforts have been dedicated to discover and manufacture protective antigens from the proper pathogen. In contrast, after nasal administration, these antigens were made known to be insufficiently immunogenic, probably for the reason of their deprived immunogenicity or the stimulation of immunological tolerance. Several approaches have been applied to evade these problems including nanotechnology-based delivery systems, adjuvant for formulations and targeting mucosal surfaces (Table 6). These strategies proved promising for potential vaccine delivery against infectious diseases.

Challenges in nasal drug delivery

With the cutting edge technological advancements the nasal delivery approach is constantly revolutionized and many of the hidden facts were revealed. In spite of everything, many issues are still in doubt for drug delivery via nasal cavity and also in the area of drug absorption of nasally delivered drugs. The scientific community is yet to explore the complete potential of nasal route for drug delivery purpose which involves perpetual series of new developments and amending theories.

The preceding sections were devoted to summarize some elementary knowledge about nasal drug delivery which clears that the challenges associated with nasal delivery differs according to the objective, i.e. local, systemic, nose to brain or vaccine delivery. Upcoming sections attempts to cover the challenges associated with particular objectives of nasal delivery.

Challenges related to physiological and pathological aspects of nasal mucosa

Given that the absorption rate for the majority of drug substances is rapid, the degree of absorption relies on physiological factors like the nasal secretion rate, ciliary movement and metabolism (Table 7; Costantino et al., 2007; Karasulu et al., 2008; Kim et al., 2009; Cros et al., 2011; Wang et al., 2012a,b). The nasal secretion and ciliary movement can collectively termed as mucociliary clearance and fluctuate according to health conditions of individual. The nasal mucociliary clearance is inversely proportional to the bioavailability of drug compounds after nasal administration, i.e. higher the nasal secretion rate and faster the

Table 6. Nanotechnology-based systems under investigation for IN vaccination.

Vaccine/Antigen	Delivery system	References
DNA vaccine	Chitosan nanoparticles	Xu et al. (2004)
Human sperm surface antigen – CD52	Liposome	Hasegawa et al. (2002)
Influenza A vaccine	Nanoemulsion	Myc et al. (2003)
Influenza subunit vaccine	N-trimethyl Chitosan nanoparticles	Amidi et al. (2007)
Influenza vaccine	Calcium phosphate nanoparticles	Knuschke et al. (2013)
Foot-and-mouth disease (FMD) vaccine	Gel	Cokcaliskan et al. (2014)
Influenza vaccine	PLGA nanoparticles	Lemoine et al. (1999)
Multivalent group A streptococcal vaccines	Liposome	Hall et al. (2004)
Ovalbumin	Liposome	Patel et al. (2008)
pDNA vaccine	Chitosan nanoparticles	Iqbal et al. (2003)
Peptide T vaccine	PLGA microspheres	Marazuela et al. (2008)
Plasmid DNA	Cationic liposomes	Wang et al. (2004)
Recombinant anthrax vaccine	Nanoemulsion	Bielinska et al. (2007)
Tetanus Toxoid vaccine	Cationic, fusogenic liposomes	Tafaghodi et al. (2008)

Table 7. Pathological conditions and their impact on nasal mucociliary clearance (Soane et al., 2001; Illum, 2006).

Pathological condition	Impact on nasal mucociliary clearance
Primary ciliary dyskinesia	Impaired: absence or dyskinetic beating cilia
Asthma	Increased: inflammatory process and irritation Decreased: epithelial damage
Cystic fibrosis	Impaired: dehydration of mucus
Viral and bacterial infections	Compromised: loss of cilia and change of mucus properties
Diabetes mellitus	Impaired: dehydration and microvascular damage

ciliary movement results in lower nasal bioavailability (Merkus et al., 2001; Soane et al., 2001; Tafaghodi et al., 2004; Illum, 2006; Boogaard et al., 2007). Formulation approaches are employed to overcome the effect of these physiological factors, for example, utilization of water miscible non-nauseating NGs and the use of anesthetic in minute quantity in the formulation (Nazar et al., 2011).

Challenges related to physicochemical and biopharmaceutical properties

It is acknowledged by several experiments that the diffusion rate of drug molecules through nasal mucosal surface is controlled by the physicochemical properties of the drug molecule. Physicochemical properties such as the ionization status and the lipophilicity of the drug molecule can have a prominent influence on the absorption rate through the nasal mucosa. Based on the explanation by researchers, it was accomplished that *in vivo* absorption of drug molecules from nasal cavity is not significantly influenced by the physicochemical properties of the drug of molecular weight of less than 300 (Mistry et al., 2009a; Malerba et al., 2011). Attributes like the size of the molecule and possibly the hydrogen bonding between the molecule and the constituents of the nasal mucosa are more significant than lipophilicity and ionization status. For instance, results with the dipeptide L-tyrosyl-L-tyrosine be evidenced that its rate of disposition after nasal administration is analogous to that observed for the L-tyrosyl-L-tyrosine methyl ester. Both of these two dipeptides have significantly different values of octanol/pH 7.4 partition coefficients, 0.02 and 3.2, for the dipeptide and the methyl ester, respectively (Costantino et al., 2007; Greimel et al., 2007).

While on the other side, the absorption rate after nasal administration is highly sensitive to drug molecules with molecular weight above 300. Resembling to gastro-intestinal (GI) absorption, the nasal absorption diminishes with the increment in molecular size. According to the above facts, the assimilation of therapeutics by nasal route most likely expected through the mediated channels of the nasal membrane. In view of the fact that the absorption rate of most drugs is hasty, the drug plasma concentration levels can be influenced and controlled by nanotechnology-based formulation advancements.

Challenges related to formulations/dosage forms

The acceptance and efficacy of a nasal formulation is affected by quite a few factors such as pH, drug concentration, osmolarity, viscosity, particle size, surfactants, physical state of dosage form and nasal clearance. Optimal consideration of these aspects demonstrates superior absorption of therapeutic agents through the nasal mucosa.

pH

The degree of nasal absorption is affected by the p*K*a value of drug and pH at the site of absorption, contributing for that as well the pH of formulation. By this point, it should be acknowledged that the pH of formulation be required to be selected in accordance with drug stability and if achievable should be secure the utmost magnitude of non-ionized form of drug.

In contrast, the pH of formulation can provoke nasal mucosal irritation and for this reason, it supposed to be comparable to that of human nasal mucosa (5.0–6.5; Mistry et al., 2009a; Vujanic et al., 2012). Moreover, the pH often avoids the bacterial escalation (Costantino et al., 2007). To assess the consequence of pH on the integrity of nasal mucosal surface, drug solutions of different pH values ranging from 2 to 12 were applied to rat nasal mucosa whose pH is 7.39 and the outcomes verified that when pH ranged from 3 to 10, negligible magnitude of proteins and enzymes were released from cells, indicative of no cellular damages. On the other hand, if pH values were lower than 3 or higher than 10, damages were observed intracellularly and at membrane level (Costantino et al., 2007; Hehar et al., 1999; Litvyakova & Baraniuk, 2001).

Drug concentration

Concentration of drug plays extremely significant function in the permeation/absorption progression of drug in the course of nasal membrane due to the damage of nasal mucosal surface. This is illustrated by the process of nasal absorption of L-tyrosine which increases with drug concentration in nasal perfusion experiments (Boek et al., 1999; Merkus et al., 2001; Costantino et al., 2007). Also, the nasal absorption of salicylic acid was found to turn down with concentration (Quraishi et al., 1997). This fall is likely due to the damage of nasal mucosa.

Osmolarity

The influence of osmolarity of the formulations on nasal absorption of the drug was studied in the rats by using model drug. The concentration of sodium chloride in the formulation has an effect on the nasal absorption of drug. The utmost absorption was accomplished at the concentration of 0.462 M; the elevated concentration of sodium chloride not merely enhances bioavailability although accompany to the toxicity to the nasal epithelium layer (Ohwaki et al., 1985).

Drugs distribution and deposition

The extent of nasal absorption is markedly affected by the distribution of drug in the nasal cavity. The approach of drug administration may possibly influence the distribution of drug in nasal cavity, which directly affects the absorption proficiency of a drug. The anatomy of nasal cavity plays an

important role as the absorption and bioavailability of the nasal formulations predominantly depends on the site of disposition. The anterior section of the nose endows with an extended nasal residential time for disposition of drug from the formulation which results in enhanced absorption (Gizurarson, 2012). Furthermore, the posterior section of nasal cavity will be responsible for the deposition of dosage forms due to mucociliary clearance and consequently results in lower bioavailability (Gizurarson et al., 1991).

Viscosity

The contact time between the nasal mucosa and formulation is lengthened by increasing the viscosity of the formulation in that way increasing the instance for permeation. However, high viscosity of formulations hampers the regular functions like ciliary beating or mucociliary clearance and as a consequence modifies the permeability of drugs (Schipper et al., 1991; Merkus & Schusler-van Hees, 1992; Mason et al., 1995; Merkus et al., 1998). This fact has been demonstrated during nasal delivery of insulin (Varshosaz et al., 2006), metoprolol (Lee et al., 2010) and acyclovir (Alsarra et al., 2009).

In contrast, higher viscosity always does not result in an increased degree of absorption. Fascinatingly, the fact was observed that the raise in viscosity results in enhanced residence time with a decline in absorption. The absorption is diminished owing to a reduced diffusion of drug from the viscous formulation (Bahadur & Pathak, 2012b). In contrast, it has also been reported that the larger therapeutic period of nasal formulations were achieved with elevated viscosity (Tas et al., 2006; Pisal et al., 2012).

Pharmaceutical form

Deposition of dosage form in different sections of nasal cavity and its retention at the site of choice, i.e. olfactory region in case of CNS delivery depends on the pharmaceutical form of delivery systems. Nasal drops are considered as the commonest and the most convenient pharmaceutical dosage form for nasal delivery, but the precise dosing control of drug to be delivered is somewhat difficult and repeatedly results in overdose (Suman, 2003; Aggarwal et al., 2004). In addition, rapid nasal drainage is also associated with nasal drops. Liquid (suspension and solution) sprays are more convenient over powder sprays for the reason that the powder sprays easily provoked the nasal mucosal irritation (Duchateau, 1987). In recent times, gel approaches have been appraised for a more precise drug delivery through nasal cavity. They lessen post-nasal spread out and anterior run-off by detaining the dosage form in nasal mucosa hence the residence time increases and mucociliary clearance diminishes (Alsarra et al., 2009). During the last years, fanatical delivery systems such as microemulsions, nanoemulsions, microspheres, liposomes and nasal films have also been formulated for better therapeutic delivery via nasal route.

Pharmaceutical excipients

Ample varieties of pharmaceutical excipients are utilized in nasal formulations according to their functions. The selection of the excipients primarily based on the requirements of the particular dosage form. Gelling agents, viscosity enhancers, solubilizers, buffer components, antioxidants, preservatives, humectants and flavoring agents or taste masking agents are an assortment of the common excipients (Merkus et al., 1991a; Merkus et al., 1999a; Illum et al., 2001; Davis & Illum, 2003). The excipients selected for a formulation required to be compatible and not to hamper the absorption of drug from nasal mucosal surface. Although, some of the excipients cause nasal irritation, thus care should be taken in the selection of excipients.

Challenges related to delivery devices

The conventional delivery devices utilized for the delivery of formulations via nasal route like droppers, sprayers, etc., are unable to take overall advantage of described potential benefits of nasal deliverance. A considerable amount of nasally administered dose is deposited on the anterior portion reinforced by skin, which is recognized as a poor site for topical as well as for systemic drugs (Duchateau, 1987; Kimbell et al., 2007; Hughes et al., 2008; Kundoor & Dalby, 2010). The deposition of topical steroids at these sites leads to common adverse effects in the form of irritation, bleeding and crusting. Drugs transported towards the nasopharynx may possibly cause unpleasant taste and irritation resulting in reduced patient compliance (Merkus et al., 2001). Conclusively, inadequate and erratic deposition in the impenetrable region covering the openings to sinuses and middle ears, as well as the olfactory region, represents a generous confront for nasal deliverance of drugs and vaccines. Development of the efficient delivery devices in particular for new advanced and expensive drugs provides a sharp tool for reliable dosing, high patient compliance and reproducible bioavailability to ensure their efficacy and safety.

On the formulation front, majority of nasal products are currently formulated as liquids and administered by metered spray pumps. The foremost hindrance associated with conventional spray pump devices is how to achieve enhanced deposition and at the same time restraining the fraction of small particles able to by-pass nasal passage and enter into the lungs as the nasal cavity anatomically designed to entrap and eliminate any foreign substance entering through this cavity (Bommer, 1999; Djupesland et al., 2004). Well-organized reformulations in combination with novel delivery devices proffer remarkable utensils for boosting effectiveness and differentiating a product from those of competitors. In addition, efficient and patient-friendly delivery devices in combination with nanotechnology-based dosage forms can support extended patent life and increase competitiveness. The risen charisma towards IN deliverance of drugs and vaccines has, however, driven on the challenge for advanced nasal delivery technologies. Disposable unit dose devices (Djupesland & Docekal, 2010) slashes the problems allied with spray pump priming and hygiene but, up to now, efficient and consistent distribution to the desired nasal segments as per the requirements, i.e. local, systemic or CNS delivery has proven difficult to conquer in practice.

Profile of an "ideal" drug contender for nasal delivery

- Appropriate solubility to provide the desired dose in a 25–150 µl volume of formulation administered per nostril; providing the therapeutic effects.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose, in general, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with drug.
- Suitable stability characteristics.

Nanotechnology-based approaches for nasal delivery

In recent times, much attention has been given to nanotechnology in many areas. In previous decade research, arena is focused on the development of nanoemulsions, liposomes, NPs, NGs and microspheres for IN drug delivery (Table 4). To improve the stability, nasal permeation and retention time of formulations, these systems are combined with enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers. The fact that how these systems improve drug absorption is not clear but it is supposed that transportation of encapsulated drug across membrane or lengthening of retention period and higher stability complement the absorption. However, the outcomes of these nanotechnology-based systems have been extremely promising when combined with the nasal delivery.

Nanoemulsions

Emulsions with nanosize droplets, typically in the range of 20–200 nm are often referred as nanoemulsions (NEs). These multicomponent systems appear transparent or translucent to the naked eyes and possess long term physical stability. Brownian motion of droplets prevent creaming or sedimenting and eventually coalescing. Small droplet size avoids any flocculation, enabling the system to remain dispersed with no phase separation. Recently, much attention has been paid to the application of NEs as drug delivery systems, since NEs are thermodynamically stable and are formed spontaneously by simple mixing of the various components.

A large number of therapeutic molecules were tested in combination of this nanosystem for nasal delivery and these studies established it as an effective carrier/adjuvant for nasal formulations (Elshafeey et al., 2009). It has been demonstrated that the nanoemulsion-based vaccines are not altered physically or chemically and retain potency following actuation with nasal spray devices (Makidon et al., 2010). In different investigations, NEs were utilized for IN delivery of influenza A vaccine (Myc et al., 2003) and recombinant anthrax vaccine (Bielinska et al., 2007).

A study on risperidone-loaded intranasal nanoemulsion for brain targeting purpose demonstrated rapid and larger extent of risperidone transport into the rat brain (Kumar et al., 2008). A variety of therapeutics like sertraline hydrochloride (Kumar et al., 2009), amiloride (Jain et al., 2011), morphine (Illum et al., 2002) etc. were investigated as NEs for their nose-to-brain targeting potential.

Nanoparticles

Nanoparticulate systems are being explored to get better drug or vaccine delivery via IN drug administration (Almeida & Alpar, 1996; Illum, 2007; Csaba et al., 2009; Ali et al., 2010). Nanoparticles (NPs) are compact colloidal particles with diameters varying from 1 to 1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached (Teijeiro-Osorio et al., 2009; Slomkowski & Gosecki, 2011). NPs may offer several advantages due to their small size, but only the smallest NPs penetrate the mucosal membrane by paracellular route and in a limited quantity as the tight junctions are in the order of 3.9–8.4 Å (Wang et al., 2009; Zhang et al., 2012).

A novel biodegradable nose-to-brain drug delivery system composed of Solanum tuberosum lectin (STL) conjugated PLGA NPs labeled with coumarin-6 demonstrated that higher brain targeting efficiency in different brain tissues than unmodified NPs (Chen et al., 2012). A similar investigation report the transport of wheat germ agglutinin conjugated PEG-PLA NPs to CNS via olfactory pathway and trigeminal nerve pathway (Liu et al., 2012). The attraction towards NPs for IN delivery is supported by the recent development of NPs containing risperidone (Patel et al., 2011), curcumin (Kundu et al., 2012), itraconazole (Chen et al., 2011), sesamol (Kakkar et al., 2011), etc.

Debatable findings are reported regarding the utilization of NPs for IN delivery of therapeutic agents (Merkus et al., 1991b; Merkus et al., 2003; Merkus & van den Berg, 2007). In fact, some research reports states that NPs do not significantly enhance the bioavailability of drug delivered by nasal route (Merkus & van den Berg, 2007). The low bioavailability due to the fact that NPs are possibly seized by macrophages in lymphoid tissues and therefore, drained into the lymphatic system and blood stream. In contrast, other investigations have advocated that NPs may be ideally suitable for the nasal delivery of vaccines (Almeida & Alpar, 1996; Mistry et al., 2009b).

Nanogels

Nanogels (NGs) are high-viscosity systems containing nanoparticulates (NPs, microcapsules, NEs, etc.) in a polymer network (Witschi & Mrsny, 1999; McDonough et al., 2007). These systems are not of much interest until the recent advancement in precise dosing devices. The advantages of NGs take account of reduced mucociliary clearance due to elevated viscosity, reduction in taste impact due to reduced post-nasal drip towards nasopharynx, reduced irritation due to soothing/emollient excipients and target delivery to mucosa for better absorption (Pisal et al., 2004a; Alsarra et al., 2009; Al-Ghananeem et al., 2011). Deposition of NGs in the nasal cavity is influenced by the mode of administration, because elevated viscosities of these systems responds in terms of deprived spreading abilities. Well-designed applicators are

required for proper spreading of NGs. Without special applicators they only occupy a narrow distribution area in the nasal cavity, where it is placed directly. To overcome the problems related to spreadability, *in situ* gelling agents are incorporated in the formulation of NGs (Pisal et al., 2004b; Varshosaz et al., 2006; Cao et al., 2009; Cai et al., 2011). These systems are appears as liquids in storage conditions but converted to gels at the site of application. This conversion is triggered by the pH (Nakamura et al., 1999), temperature (Majithiya et al., 2006; Mahajan et al., 2012), presence of any other ionic or biological component, etc.

Liposomes

Liposomes are composed of phospholipids bilayers enclosing one or more aqueous compartments in which drugs and other materials can be assimilated. Numerous advantages are offered by liposomal drug delivery systems in terms of efficient encapsulation of small and bulky molecules with a wide range of hydrophilicity. Some research reports stated that liposomes supplement nasal absorption of peptides (Wearley, 1991; Shahiwala & Misra, 2006), for example, insulin (Muramatsu et al., 1999) and calcitonin (Bijani et al., 2012) by intensifying their membrane penetration. The enhanced absorption is attributed to the elongated retention period of peptides, shielding of encapsulated peptides from enzymatic deprivation and mucosal membrane distraction. Insulin-loaded chitosan and carbopol liposomes confirmed the effectiveness of novel mucoadhesive multivesicular liposomes after IN administration in rats (Muramatsu et al., 1999).

In addition, usefulness of liposomes was also disclosed for the delivery of influenza vaccine (Chiou et al., 2009) and non-peptide drugs such as nicardipine via nasal route (Visor et al., 1986). Liposomes can be assimilated in a range of formulations. For instance, liposomal suspension of levonorgestrel exhibits a prompt response and sustained action subsequent to administration through nasal cavity (Shahiwala & Misra, 2004). Furthermore, acyclovir-loaded liposomes when studied as gel formulation for nasal delivery offer promising results in comparison with free drug suspended in gel (Alsarra et al., 2009). By varying size or phospholipid composition, liposomes can be tailored according to the properties of drug. These parameters have a significant impact on nasal delivery of drugs. The drug can be entrapped within the aqueous pocket or amalgamated to the exterior surface. The extensive study of liposomes opens the new opportunities for the nasal delivery of therapeutics and vaccines in humans.

Microspheres

As an effectual formulation microspheres are comprehensively applied for the delivery of therapeutics by nasal route (Harikarnpakdee et al., 2006; Hafner et al., 2007; Gavini et al., 2009; Kang et al., 2009; Patil & Sawant, 2011). To combat with mucociliary clearance, mucoadhesive polymers like chitosan (Illum et al., 2001; Hafner et al., 2007; Gungor et al., 2010b), gelatin (Wang et al., 2006), alginates (Patil et al., 2012), etc., are included during formulation resulting in longer contact time for better absorption of drugs. Furthermore, microspheres also possess an effective delivery system for the drugs vulnerable for enzymatic degradation and may also provide sustained drug release, if required (Cerchiara et al., 2005; Gungor et al., 2010a). Gelatin microspheres of insulin exhibited a significant hypoglycemic effect in rats after nasal administration in dry powder form, in comparison to the suspension of insulin (Wang et al., 2006). Alginate/chitosan microspheres containing metoclopramide indicate the opening of tight junctions of nasal epithelium and also accredited as promising mucoadhesive nasal carriers (Gavini et al., 2008, 2009).

Carbon nanotubes

Carbon nanotubes (CNTs) are emergent tools in the province of nanomedicine and nanobiotechnology. This is because they can be easily manipulated and modified by encapsulation with biopolymers or by covalent linking of solubilizing groups to the external walls and tips. CNTs exclusively composed of carbon atoms organized in a series of condensed benzene rings, which are rolled up into a tubular configuration. CNTs can be classified as single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs; Kumar et al., 2014). CNTs can also be explored for nose to brain targeted drug delivery by considering surface engineering approach so as to enhance the bioavailability and therapeutic efficacy of therapeutic agents that otherwise finds difficulty for delivery by any other route.

Quantum dots

A quantum dot (QD) is a nano-crystal comprised of semiconductor ingredients which exhibit quantum mechanical properties due to their nano-scale magnitude. The realization of QDs application in imaging, sensing and detection has inspired scientific community to extend this platform for drug delivery research. Due to their potential to elucidate the pharmacokinetics and pharmacodynamics of therapeutic agents, the development of traceable drug delivery carriers is one of the most promising applications of QDs to postulate the design principles for drug carrier engineering (Lifeng & Xiaohu, 2008).

Cadmium QDs are known to have neurological effects but recently their potential for direct nose to brain delivery has been revealed in a study (Laurie et al., 2014). This study shows rapid uptake of QDs by brain/olfactory bulb via axonal transport following short-term inhalation. The study claims that it is the first attempt which demonstrate the IN delivery of QDs for nose to brain transport.

Conclusion

Nanosystems by means of diverse compositions and biological possessions have been expansively scrutinized for drug delivery applications via nasal route. It appears that nanotechnology-based drug delivery systems hold great potential to overcome some of the barriers in IN delivery. Nanosystems are efficiently taken up by nasal mucosa and therefore, may possibly be used as efficient transport and delivery systems for therapeutics through nasal mucosa. An efficient approach for attaining effective treatment would

be to prudently build-up nanosystems based on the indulgent of their interactions with the nasal environment, mechanism and site of drug action, drug retention, multiple drug administration and pathobiology of the disease under consideration.

The era of nasal drug delivery is growing; however, new efforts are needed to make this route of delivery more efficient and popular. Considering the widespread interest in nasal drug delivery and the potential benefits of IN administration, it is expected that novel nasal products will continue to reach the market. They will include not only drugs for acute and chronic diseases, but also novel nasal vaccines with better local or systemic protection against infections. The development of drugs for directly target the brain to attain a good therapeutic effect in CNS with reduced systemic side effects is feasible. However, it was also stated that IN route presents several limitations which must be overcome to develop a successful nasal medicine.

Acknowledgment

One of the authors, Amrish Kumar, gratefully acknowledges University Grants Commission, New Delhi, India for awarding Senior Research Fellowship for his Doctoral Degree.

Declaration of interest

The authors report no declarations of interest.

References

Aggarwal R, Cardozo A, Homer JJ. (2004). The assessment of topical nasal drug distribution. Clin Otolaryngol Allied Sci 29:201–5.

Al-Ghananeem AM, Malkawi AH, Crooks PA. (2011). Bioavailability of Delta(9)-tetrahydrocannabinol following intranasal administration of a mucoadhesive gel spray delivery system in conscious rabbits. Drug Dev Ind Pharm 37:329–34.

Al-Ghananeem AM, Saeed H, Florence R, et al. (2010). Intranasal drug delivery of didanosine-loaded chitosan nanoparticles for brain targeting; an attractive route against infections caused by AIDS viruses. J Drug Target 18:381–8.

Ali J, Ali M, Baboota S, et al. (2010). Potential of nanoparticulate drug delivery systems by intranasal administration. Curr Pharm Des 16: 1644–53.

Almeida AJ, Alpar HO. (1996). Nasal delivery of vaccines. J Drug Target 3:455–67.

Alsarra IA, Hamed AY, Mahrous GM, et al. (2009). Mucoadhesive polymeric hydrogels for nasal delivery of acyclovir. Drug Dev Ind Pharm 35:352–62.

Amidi M, Romeijn SG, Verhoef JC, et al. (2007). N-trimethyl chitosan (TMC) nanoparticles loaded with influenza subunit antigen for intranasal vaccination: biological properties and immunogenicity in a mouse model. Vaccine 25:144–53.

Arora P, Sharma S, Garg S. (2002). Permeability issues in nasal drug delivery. Drug Discov Today 7:967–75.

Bacon A, Makin J, Sizer PJ, et al. (2000). Carbohydrate biopolymers enhance antibody responses to mucosally delivered vaccine antigens. Infect Immun 68:5764–70.

Bahadur S, Pathak K. (2012a). Buffered nanoemulsion for nose to brain delivery of ziprasidone hydrochloride: preformulation and pharmacodynamic evaluation. Curr Drug Deliv 9:596–607.

Bahadur S, Pathak K. (2012b). Physicochemical and physiological considerations for efficient nose-to-brain targeting. Expert Opin Drug Deliv 9:19–31.

Balle VH, Illum P, Meistrup-Larsen U, Olesen KF. (1979). Disodium cromoglycate in the treatment of allergic conditions of the nose. Ugeskr Laeger 141:1906–8.

Belgamwar VS, Patel HS, Joshi AS, et al. (2011). Design and development of nasal mucoadhesive microspheres containing tramadol HCl for CNS targeting. Drug Deliv 18:353–60.

Bielinska AU, Janczak KW, Landers JJ, et al. (2007). Mucosal immunization with a novel nanoemulsion-based recombinant anthrax protective antigen vaccine protects against *Bacillus anthracis* spore challenge. Infect Immun 75:4020–9.

Bijani C, Arnarez C, Brasselet S, et al. (2012). Stability and structure of protein-lipoamino acid colloidal particles: toward nasal delivery of pharmaceutically active proteins. Langmuir 28:5783–94.

Bitter C, Suter-Zimmermann K, Surber C. (2011). Nasal drug delivery in humans. Curr Probl Dermatol 40:20–35.

Boek WM, Romeijn SG, Graamans K, et al. (1999). Validation of animal experiments on ciliary function in vitro. II. The influence of absorption enhancers, preservatives and physiologic saline. Acta Otolaryngol 119:98–101.

Bommer R. (1999). Latest advances in nasal drug-delivery technology. Med Device Technol 10:22–8.

Boogaard R, de Jongste JC, Merkus PJ. (2007). Pharmacotherapy of impaired mucociliary clearance in non-CF pediatric lung disease. A review of the literature. Pediatr Pulmonol 42:989–1001.

Bragagni M, Mennini N, Ghelardini C, Mura P. (2012). Development and characterization of niosomal formulations of doxorubicin aimed at brain targeting. J Pharm Pharm Sci 15:184–96.

Brave A, Hallengard D, Schroder U, et al. (2008). Intranasal immunization of young mice with a multigene HIV-1 vaccine in combination with the N3 adjuvant induces mucosal and systemic immune responses. Vaccine 26:5075–8.

Brooking J, Davis SS, Illum L. (2001). Transport of nanoparticles across the rat nasal mucosa. J Drug Target 9:267–79.

Caban S, Capan Y, Couvreur P, Dalkara T. (2012). Preparation and characterization of biocompatible chitosan nanoparticles for targeted brain delivery of peptides. Methods Mol Biol 846:321–32.

Cai Z, Song X, Sun F, et al. (2011). Formulation and evaluation of in situ gelling systems for intranasal administration of gastrodin. AAPS PharmSciTech 12:1102–9.

Cao SL, Ren XW, Zhang QZ, et al. (2009). In situ gel based on gellan gum as new carrier for nasal administration of mometasone furoate. Int J Pharm 365:109–15.

Cerchiara T, Luppi B, Chidichimo G, et al. (2005). Chitosan and poly(methyl vinyl ether-co-maleic anhydride) microparticles as nasal sustained delivery systems. Eur J Pharm Biopharm 61:195–200.

Chandler SG, Thomas NW, Illum L. (1994). Nasal absorption in the rat. III. Effect of lysophospholipids on insulin absorption and nasal histology. Pharm Res 11:1623–30.

Charlton ST, Davis SS, Illum L. (2007). Nasal administration of an angiotensin antagonist in the rat model: effect of bioadhesive formulations on the distribution of drugs to the systemic and central nervous systems. Int J Pharm 338:94–103.

Chen J, Zhang C, Liu Q, et al. (2012). Solanum tuberosum lectin-conjugated PLGA nanoparticles for nose-to-brain delivery: in vivo and in vitro evaluations. J Drug Target 20:174–84.

Chen W, Zhan C, Gu B, et al. (2011). Targeted brain delivery of itraconazole via RVG29 anchored nanoparticles. J Drug Target 19: 228–34.

Chiou CJ, Tseng LP, Deng MC, et al. (2009). Mucoadhesive liposomes for intranasal immunization with an avian influenza virus vaccine in chickens. Biomaterials 30:5862–8.

Chung SW, Hil-lal TA, Byun Y. (2012). Strategies for non-invasive delivery of biologics. J Drug Target 20:481–501.

Cokcaliskan C, Ozyoruk F, Gursoy RN, et al. (2014). Chitosan-based systems for intranasal immunization against foot-and-mouth disease. Pharm Dev Technol 19:181–8.

Costantino HR, Illum L, Brandt G, et al. (2007). Intranasal delivery: physicochemical and therapeutic aspects. Int J Pharm 337:1–24.

Critchley H, Davis SS, Farraj NF, Illum L. (1994). Nasal absorption of desmopressin in rats and sheep. Effect of a bioadhesive microsphere delivery system. J Pharm Pharmacol 46:651–6.

Cros CD, Toth I, Blanchfield JT. (2011). Lipophilic derivatives of leu-enkephalinamide: in vitro permeability, stability and in vivo nasal delivery. Bioorg Med Chem 19:1528–34.

Csaba N, Garcia-Fuentes M, Alonso MJ. (2009). Nanoparticles for nasal vaccination. Adv Drug Deliv Rev 61:140–57.

Davis SS, Illum L. (2003). Absorption enhancers for nasal drug delivery. Clin Pharmacokinet 42:1107–28.

Deurloo MJ, Hermens WA, Romeyn SG, et al. (1989). Absorption enhancement of intranasally administered insulin by sodium taurodihydrofusidate (STDHF) in rabbits and rats. Pharm Res 6:853–6.

Djupesland PG, Docekal P. (2010). Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: a randomised, placebo-controlled study. Cephalalgia 30:933–42.

Djupesland PG, Skretting A, Winderen M, Holand T. (2004). Bi-directional nasal delivery of aerosols can prevent lung deposition. J Aerosol Med 17:249–59.

Douglas SJ, Davis SS, Illum L. (1987). Nanoparticles in drug delivery. Crit Rev Ther Drug Carrier Syst 3:233–61.

Duchateau GS. (1987). Studies on nasal drug delivery. Pharm Weekbl Sci 9:326–8.

Duchateau GS, Zuidema J, Merkus FW. (1986a). Bioavailability of propranolol after oral, sublingual, and intranasal administration. Pharm Res 3:108–11.

Duchateau GS, Zuidema J, Merkus FW. (1986b). The in vitro and in vivo effect of a new non-halogenated corticosteroid – budesonide – aerosol on human ciliary epithelial function. Allergy 41:260–5.

Duquesnoy C, Mamet JP, Sumner D, Fuseau E. (1998). Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. Eur J Pharm Sci 6:99–104.

Elshafeey AH, Bendas ER, Mohamed OH. (2009). Intranasal microemulsion of sildenafil citrate: in vitro evaluation and in vivo pharmacokinetic study in rabbits. AAPS PharmSciTech 10:361–7.

Eskandari S, Varshosaz J, Minaiyan M, Tabbakhian M. (2011). Brain delivery of valproic acid via intranasal administration of nanostructured lipid carriers: in vivo pharmacodynamic studies using rat electroshock model. Int J Nanomedicine 6:363–71.

Eyles JE, Sharp GJ, Williamson ED, et al. (1998a). Intra nasal administration of poly-lactic acid microsphere co-encapsulated Yersinia pestis subunits confers protection from pneumonic plague in the mouse. Vaccine 16:698–707.

Eyles JE, Spiers ID, Williamson ED, Alpar HO. (1998b). Analysis of local and systemic immunological responses after intra-tracheal, intranasal and intra-muscular administration of microsphere co-encapsulated Yersinia pestis sub-unit vaccines. Vaccine 16:2000–9.

Fazil M, Md S, Haque S, et al. (2012). Development and evaluation of rivastigmine loaded chitosan nanoparticles for brain targeting. Eur J Pharm Sci 47:6–15.

Gaillard PJ, Appeldoorn CC, Rip J, et al. (2012). Enhanced brain delivery of liposomal methylprednisolone improved therapeutic efficacy in a model of neuroinflammation. J Control Release 164: 364–9.

Gavini E, Rassu G, Haukvik T, et al. (2009). Mucoadhesive microspheres for nasal administration of cyclodextrins. J Drug Target 17: 168–79.

Gavini E, Rassu G, Muzzarelli C, et al. (2008). Spray-dried microspheres based on methylpyrrolidinone chitosan as new carrier for nasal administration of metoclopramide. Eur J Pharm Biopharm 68: 245–52.

Gizurarson S. (2012). Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Deliv 9:566–82.

Gizurarson S, Rasmussen SN, Larsen F. (1991). Pharmacokinetics of intranasal drug administration: the influence of some biological factors. J Pharm Sci 80:505–6.

Greimel A, Bernkop-Schnurch A, Del Curto MD, D'Antonio M. (2007). Transport characteristics of a beta sheet breaker peptide across excised bovine nasal mucosa. Drug Dev Ind Pharm 33:71–7.

Gungor S, Okyar A, Erturk-Toker S, et al. (2010a). Ondansetron-loaded biodegradable microspheres as a nasal sustained delivery system: in vitro/in vivo studies. Pharm Dev Technol 15:258–65.

Gungor S, Okyar A, Erturk-Toker S, et al. (2010b). Ondansetron-loaded chitosan microspheres for nasal antiemetic drug delivery: an alternative approach to oral and parenteral routes. Drug Dev Ind Pharm 36: 806–13.

Hafner A, Filipovic-Grcic J, Voinovich D, Jalsenjak I. (2007). Development and in vitro characterization of chitosan-based microspheres for nasal delivery of promethazine. Drug Dev Ind Pharm 33: 427–36.

Hall MA, Stroop SD, Hu MC, et al. (2004). Intranasal immunization with multivalent group A streptococcal vaccines protects mice against intranasal challenge infections. Infect Immun 72:2507–12.

Harikarnpakdee S, Lipipun V, Sutanthavibul N, Ritthidej GC. (2006). Spray-dried mucoadhesive microspheres: preparation and transport through nasal cell monolayer. AAPS PharmSciTech 7:E79–88.

Hasegawa A, Fu Y, Koyama K. (2002). Nasal immunization with diphtheria toxoid conjugated-CD52 core peptide induced specific antibody production in genital tract of female mice. Am J Reprod Immunol 48:305–11.

He P, Davis SS, Illum L. (1999). Sustained release chitosan microspheres prepared by novel spray drying methods. J Microencapsul 16:343–55.

Hehar SS, Mason JD, Stephen AB, et al. (1999). Twenty-four hour ambulatory nasal pH monitoring. Clin Otolaryngol Allied Sci 24: 24–5.

Hinchcliffe M, Illum L. (1999). Intranasal insulin delivery and therapy. Adv Drug Deliv Rev 35:199–234.

Hu KL, Mei N, Feng L, Jiang XG. (2009). Hydrophilic nasal gel of lidocaine hydrochloride. 2nd communication: improved bioavailability and brain delivery in rats with low ciliotoxicity. Arzneimittelforschung 59:635–40.

Hughes R, Watterson J, Dickens C, et al. (2008). Development of a nasal cast model to test medicinal nasal devices. Proc Inst Mech Eng H 222: 1013–22.

Illum L. (1991). The nasal delivery of peptides and proteins. Trends Biotechnol 9:284–9.

Illum L. (2000). Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 11:1–18.

Illum L. (2002). Nasal drug delivery: new developments and strategies. Drug Discov Today 7:1184–9.

Illum L. (2003). Nasal drug delivery–possibilities, problems and solutions. J Control Release 87:187–98.

Illum L. (2004). Is nose-to-brain transport of drugs in man a reality? J Pharm Pharmacol 56:3–17.

Illum L. (2006). Nasal clearance in health and disease. J Aerosol Med 19: 92–9.

Illum L. (2007). Nanoparticulate systems for nasal delivery of drugs: a real improvement over simple systems? J Pharm Sci 96:473–83.

Illum L. (2012). Nasal drug delivery – recent developments and future prospects. J Control Release 161:254–63.

Illum L, Davis SS. (1991). Drug delivery. Curr Opin Biotechnol 2:254–9.

Illum L, Davis SS. (2001). Nasal vaccination: a non-invasive vaccine delivery method that holds great promise for the future. Adv Drug Deliv Rev 51:1–3.

Illum L, Jabbal-Gill I, Hinchcliffe M, et al. (2001). Chitosan as a novel nasal delivery system for vaccines. Adv Drug Deliv Rev 51: 81–96.

Illum L, Watts P, Fisher AN, et al. (2002). Intranasal delivery of morphine. J Pharmacol Exp Ther 301:391–400.

Illum P, Balle V. (1978). Immunoglobulins in nasal secretions and nasal mucosa in perennial rhinitis. Acta Otolaryngol 86:135–41.

Iqbal M, Lin W, Jabbal-Gill I, et al. (2003). Nasal delivery of chitosan-DNA plasmid expressing epitopes of respiratory syncytial virus (RSV) induces protective CTL responses in BALB/c mice. Vaccine 21: 1478–85.

Jain N, Akhter S, Jain GK, et al. (2011). Antiepileptic intranasal Amiloride loaded mucoadhesive nanoemulsion: development and safety assessment. J Biomed Nanotechnol 7:142–3.

Jain R, Nabar S, Dandekar P, et al. (2010a). Formulation and evaluation of novel micellar nanocarrier for nasal delivery of sumatriptan. Nanomedicine (Lond) 5:575–87.

Jain R, Nabar S, Dandekar P, Patravale V. (2010b). Micellar nanocarriers: potential nose-to-brain delivery of zolmitriptan as novel migraine therapy. Pharm Res 27:655–64.

Jayachandra BR, Dayal PP, Pawar K, Singh M. (2011). Nose-to-brain transport of melatonin from polymer gel suspensions: a microdialysis study in rats. J Drug Target 19:731–40.

Jones N. (2001). The nose and paranasal sinuses physiology and anatomy. Adv Drug Deliv Rev 51:5–19.

Jones NS, Quraishi S, Mason JD. (1997). The nasal delivery of systemic drugs. Int J Clin Pract 51:308–11.

Joshi AS, Patel HS, Belgamwar VS, et al. (2012). Solid lipid nanoparticles of ondansetron HCl for intranasal delivery: development, optimization and evaluation. J Mater Sci Mater Med 23: 2163–75.

Jug M, Becirevic-Lacan M. (2008). Development of a cyclodextrin-based nasal delivery system for lorazepam. Drug Dev Ind Pharm 34: 817–26.

Kakkar V, Mishra AK, Chuttani K, et al. (2011). Delivery of sesamol-loaded solid lipid nanoparticles to the brain for menopause-related emotional and cognitive central nervous system derangements. Rejuvenation Res 14:597–604.
Kang ML, Cho CS, Yoo HS. (2009). Application of chitosan microspheres for nasal delivery of vaccines. Biotechnol Adv 27:857–65.
Kantar A. (2010). Targeting the nasal cavity in rhinitis and sinusitis. Int J Immunopathol Pharmacol 23:67–9.
Karasulu HY, Sanal ZE, Sozer S, et al. (2008). Permeation studies of indomethacin from different emulsions for nasal delivery and their possible anti-inflammatory effects. AAPS PharmSciTech 9:342–8.
Kim TK, Kang W, Chun IK, et al. (2009). Pharmacokinetic evaluation and modeling of formulated levodopa intranasal delivery systems. Eur J Pharm Sci 38:525–32.
Kimbell JS, Segal RA, Asgharian B, et al. (2007). Characterization of deposition from nasal spray devices using a computational fluid dynamics model of the human nasal passages. J Aerosol Med 20: 59–74.
Knuschke T, Sokolova V, Rotan O, et al. (2013). Immunization with biodegradable nanoparticles efficiently induces cellular immunity and protects against influenza virus infection. J Immunol 190:6221–9.
Kumar A, Sharma P, Chaturvedi A, et al. (2009). Formulation development of sertraline hydrochloride microemulsion for intranasal delivery. Int J ChemTech Res 1:941–7.
Kumar M, Misra A, Babbar AK, et al. (2008). Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm 358:285–91.
Kumar R, Dhanawat M, Kumar S, et al. (2014). Carbon nanotubes: a potential concept for drug delivery applications. Recent Pat Drug Deliv Formul 8:12–26.
Kundoor V, Dalby RN. (2010). Assessment of nasal spray deposition pattern in a silicone human nose model using a color-based method. Pharm Res 27:30–6.
Kundu P, Mohanty C, Sahoo SK. (2012). Antiglioma activity of curcumin-loaded lipid nanoparticles and its enhanced bioavailability in brain tissue for effective glioblastoma therapy. Acta Biomater 8: 2670–87.
Laurie E, Hopkins ES, Patchin PC, et al. (2014). Nose-to-brain transport of aerosolized quantum dots following acute exposure. Nanotoxicology 8:885–93.
Lee KR, Maeng HJ, Chae JB, et al. (2010). Lack of a primary physicochemical determinant in the direct transport of drugs to the brain after nasal administration in rats: potential involvement of transporters in the pathway. Drug Metab Pharmacokinet 25:430–41.
Lemoine D, Deschuyteneer M, Hogge F, Preat V. (1999). Intranasal immunization against influenza virus using polymeric particles. J Biomater Sci Polym Ed 10:805–25.
Lifeng Q, Xiaohu G. (2008). Emerging application of quantum dots for drug delivery and therapy. Expert Opin Drug Deliv 5:263–7.
Lipworth BJ, Jackson CM. (2000). Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf 23:11–33.
Litvyakova LI, Baraniuk JN. (2001). Nasal provocation testing: a review. Ann Allergy Asthma Immunol 86:355–64.
Liu Q, Shen Y, Chen J, et al. (2012). Nose-to-brain transport pathways of wheat germ agglutinin conjugated PEG-PLA nanoparticles. Pharm Res 29:546–58.
Luppi B, Bigucci F, Corace G, et al. (2011). Albumin nanoparticles carrying cyclodextrins for nasal delivery of the anti-Alzheimer drug tacrine. Eur J Pharm Sci 44:559–65.
Mahajan HS, Tyagi V, Lohiya G, Nerkar P. (2012). Thermally reversible xyloglucan gels as vehicles for nasal drug delivery. Drug Deliv 19: 270–6.
Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RS. (2006). Thermoreversible-mucoadhesive gel for nasal delivery of sumatriptan. AAPS PharmSciTech 7:E80–6.
Makidon PE, Nigavekar SS, Bielinska AU, et al. (2010). Characterization of stability and nasal delivery systems for immunization with nanoemulsion-based vaccines. J Aerosol Med Pulm Drug Deliv 23:77–89.
Malerba F, Paoletti F, Capsoni S, Cattaneo A. (2011). Intranasal delivery of therapeutic proteins for neurological diseases. Expert Opin Drug Deliv 8:1277–96.
Marazuela EG, Rodriguez R, Fernandez-Garcia H, et al. (2008). Intranasal immunization with a dominant T-cell epitope peptide of a major allergen of olive pollen prevents mice from sensitization to the whole allergen. Mol Immunol 45:438–45.
Marttin E, Romeijn SG, Verhoef JC, Merkus FW. (1997). Nasal absorption of dihydroergotamine from liquid and powder formulations in rabbits. J Pharm Sci 86:802–7.
Marttin E, Verhoef JC, Merkus FW. (1998). Efficacy, safety and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs. J Drug Target 6:17–36.
Mason JD, Aspden TJ, Adler J, et al. (1995). Measurement of nasal mucociliary transport rates on the isolated human inferior turbinate. Clin Otolaryngol Allied Sci 20:530–5.
McDonough JA, Persyn JT, Nino JA, et al. (2007). Microcapsule-gel formulation of promethazine HCl for controlled nasal delivery: a motion sickness medication. J Microencapsul 24:109–16.
McNeela EA, Jabbal-Gill I, Illum L, et al. (2004). Intranasal immunization with genetically detoxified diphtheria toxin induces T cell responses in humans: enhancement of Th2 responses and toxin-neutralizing antibodies by formulation with chitosan. Vaccine 22: 909–14.
McNeela EA, O'Connor D, Jabbal-Gill I, et al. (2000). A mucosal vaccine against diphtheria: formulation of cross reacting material (CRM(197)) of diphtheria toxin with chitosan enhances local and systemic antibody and Th2 responses following nasal delivery. Vaccine 19:1188–98.
Merkus FW, Schusler-van Hees MT. (1992). Influence of levocabastine suspension on ciliary beat frequency and mucociliary clearance. Allergy 47:230–3.
Merkus FW, van den Berg MP. (2007). Can nasal drug delivery bypass the blood-brain barrier?: questioning the direct transport theory. Drugs R D 8:133–44.
Merkus FW, Verhoef JC, Marttin E, et al. (1999a). Cyclodextrins in nasal drug delivery. Adv Drug Deliv Rev 36:41–57.
Merkus FW, Verhoef JC, Romeijn SG, Schipper NG. (1991a). Absorption enhancing effect of cyclodextrins on intranasally administered insulin in rats. Pharm Res 8:588–92.
Merkus FW, Verhoef JC, Romeijn SG, Schipper NG. (1991b). Interspecies differences in the nasal absorption of insulin. Pharm Res 8:1343 (PMID: 1796056).
Merkus FW, Verhoef JC, Schipper NG, Marttin E. (1998). Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Deliv Rev 29:13–38.
Merkus P, Guchelaar HJ, Bosch DA, Merkus FW. (2003). Direct access of drugs to the human brain after intranasal drug administration? Neurology 60:1669–71.
Merkus P, Romeijn SG, Verhoef JC, et al. (2001). Classification of cilio-inhibiting effects of nasal drugs. Laryngoscope 111:595–602.
Merkus PJ, de Jongste JC. (2006). Inhaled corticosteroids and long term outcome in adults with asthma. Thorax 61:1011 (PMCID: PMC2121169).
Merkus PJ, Hazelzet JA, de Jongste JC. (1999b). Inhalation corticosteroids and the growth of asthmatic children. Ned Tijdschr Geneeskd 143:2547 (PMID: 10627761).
Mistry A, Glud SZ, Kjems J, et al. (2009a). Effect of physicochemical properties on intranasal nanoparticle transit into murine olfactory epithelium. J Drug Target 17:543–52.
Mistry A, Stolnik S, Illum L. (2009b). Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm 379:146–57.
Muramatsu K, Maitani Y, Takayama K, Nagai T. (1999). The relationship between the rigidity of the liposomal membrane and the absorption of insulin after nasal administration of liposomes modified with an enhancer containing insulin in rabbits. Drug Dev Ind Pharm 25:1099–105.
Myc A, Kukowska-Latallo JF, Bielinska AU, et al. (2003). Development of immune response that protects mice from viral pneumonitis after a single intranasal immunization with influenza A virus and nanoemulsion. Vaccine 21:3801–14.
Nakamura K, Maitani Y, Lowman AM, et al. (1999). Uptake and release of budesonide from mucoadhesive, pH-sensitive copolymers and their application to nasal delivery. J Control Release 61:329–35.
Nazar H, Fatouros DG, van der Merwe SM, et al. (2011). Thermosensitive hydrogels for nasal drug delivery: the formulation and characterisation of systems based on N-trimethyl chitosan chloride. Eur J Pharm Biopharm 77:225–32.

Ohwaki T, Ando H, Watanabe S, Miyake Y. (1985). Effects of dose, pH, and osmolarity on nasal absorption of secretin in rats. J Pharm Sci 74: 550–2.

Ozsoy Y, Gungor S, Cevher E. (2009). Nasal delivery of high molecular weight drugs. Molecules 14:3754–79.

Patel GB, Ponce A, Zhou H, Chen W. (2008). Structural characterization of archaeal lipid mucosal vaccine adjuvant and delivery (AMVAD) formulations prepared by different protocols and their efficacy upon intranasal immunization of mice. J Liposome Res 18:127–43.

Patel S, Chavhan S, Soni H, et al. (2011). Brain targeting of risperidone-loaded solid lipid nanoparticles by intranasal route. J Drug Target 19: 468–74.

Patil SB, Kaul A, Babbar A, et al. (2012). In vivo evaluation of alginate microspheres of carvedilol for nasal delivery. J Biomed Mater Res B Appl Biomater 100:249–55.

Patil SB, Sawant KK. (2011). Chitosan microspheres as a delivery system for nasal insufflation. Colloids Surf B Biointerfaces 84:384–9.

Pires A, Fortuna A, Alves G, Falcao A. (2009). Intranasal drug delivery: how, why and what for? J Pharm Pharm Sci 12:288–311.

Pisal PB, Patil SS, Pokharkar VB. (2012). Rheological investigation and its correlation with permeability coefficient of drug loaded carbopol gel: influence of absorption enhancers. Drug Dev Ind Pharm 39: 593–9.

Pisal S, Shelke V, Mahadik K, Kadam S. (2004a). Effect of organogel components on in vitro nasal delivery of propranolol hydrochloride. AAPS PharmSciTech 5:92–100.

Pisal SS, Paradkar AR, Mahadik KR, Kadam SS. (2004b). Pluronic gels for nasal delivery of Vitamin B12. Part I: preformulation study. Int J Pharm 270:37–45.

Quraishi MS, Jones NS, Mason JD. (1997). The nasal delivery of drugs. Clin Otolaryngol Allied Sci 22:289–301.

Rajadhyaksha M, Boyden T, Liras J, et al. (2011). Current advances in delivery of biotherapeutics across the blood-brain barrier. Curr Drug Discov Technol 8:87–101.

Read RC, Naylor SC, Potter CW, et al. (2005). Effective nasal influenza vaccine delivery using chitosan. Vaccine 23:4367–74.

Ruan Y, Yao L, Zhang B, et al. (2011). Antinociceptive properties of nasal delivery of neurotoxin-loaded nanoparticles coated with polysorbate-80. Peptides 32:1526–9.

Salama HA, Mahmoud AA, Kamel AO, et al. (2012). Brain delivery of olanzapine by intranasal administration of transfersomal vesicles. J Liposome Res 22:336–45.

Scheerlinck JP, Gekas S, Yen HH, et al. (2006). Local immune responses following nasal delivery of an adjuvanted influenza vaccine. Vaccine 24:3929–36.

Schipper NG, Romeijn SG, Verhoef J, Merkus FW. (1994). Hypocalcemic effect of salmon calcitonin following single and repeated nasal and intravenous administration in young rabbits. Calcif Tissue Int 54:50–5.

Schipper NG, Verhoef JC, Merkus FW. (1991). The nasal mucociliary clearance: relevance to nasal drug delivery. Pharm Res 8:807–14.

Seju U, Kumar A, Sawant KK. (2011). Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: in vitro and in vivo studies. Acta Biomater 7:4169–76.

Shahiwala A, Misra A. (2004). Nasal delivery of levonorgestrel for contraception: an experimental study in rats. Fertil Steril 81:893–8.

Shahiwala A, Misra A. (2006). Preliminary investigation of the nasal delivery of liposomal leuprorelin acetate for contraception in rats. J Pharm Pharmacol 58:19–26.

Slomkowski S, Gosecki M. (2011). Progress in nanoparticulate systems for peptide, proteins and nucleic acid drug delivery. Curr Pharm Biotechnol 12:1823–39.

Slot WB, Merkus FW, Van Deventer SJ, Tytgat GN. (1997). Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. Gastroenterology 113:430–3.

Smith JH, Papania M, Knaus D, et al. (2012). Nebulized live-attenuated influenza vaccine provides protection in ferrets at a reduced dose. Vaccine 30:3026–33.

Soane RJ, Carney AS, Jones NS, et al. (2001). The effect of the nasal cycle on mucociliary clearance. Clin Otolaryngol Allied Sci 26:9–15.

Suman JD. (2003). Nasal drug delivery. Expert Opin Biol Ther 3: 519–23.

Tafaghodi M, Abolghasem Sajadi TS, Jaafari MR, et al. (2004). Evaluation of the clearance characteristics of various microspheres in the human nose by gamma-scintigraphy. Int J Pharm 280:125–35.

Tafaghodi M, Jaafari MR, Tabassi SA. (2008). Nasal immunization studies by cationic, fusogenic and cationic-fusogenic liposomes encapsulated with tetanus toxoid. Curr Drug Deliv 5:108–13.

Tas C, Ozkan CK, Savaser A, et al. (2006). Nasal absorption of metoclopramide from different Carbopol 981 based formulations: in vitro, ex vivo and in vivo evaluation. Eur J Pharm Biopharm 64: 246–54.

Teijeiro-Osorio D, Remunan-Lopez C, Alonso MJ. (2009). New generation of hybrid poly/oligosaccharide nanoparticles as carriers for the nasal delivery of macromolecules. Biomacromolecules 10:243–9.

van Asselt DZ, Merkus FW, Russel FG, Hoefnagels WH. (1998). Nasal absorption of hydroxocobalamin in healthy elderly adults. Br J Clin Pharmacol 45:83–6.

van der Kuy PH, Lohman JJ, Hooymans PM, et al. (1999). Bioavailability of intranasal formulations of dihydroergotamine. Eur J Clin Pharmacol 55:677–80.

Varshosaz J, Sadrai H, Heidari A. (2006). Nasal delivery of insulin using bioadhesive chitosan gels. Drug Deliv 13:31–8.

Veronesi MC, Kubek DJ, Kubek MJ. (2011). Intranasal delivery of neuropeptides. Methods Mol Biol 789:303–12.

Visor GC, Bajka E, Benjamin E. (1986). Intranasal delivery of nicardipine in the rat. J Pharm Sci 75:44–6.

Vujanic A, Sutton P, Snibson KJ, et al. (2012). Mucosal vaccination: lung versus nose. Vet Immunol Immunopathol 148:172–7.

Wang D, Christopher ME, Nagata LP, et al. (2004). Intranasal immunization with liposome-encapsulated plasmid DNA encoding influenza virus hemagglutinin elicits mucosal, cellular and humoral immune responses. J Clin Virol 31:S99–106.

Wang J, Tabata Y, Morimoto K. (2006). Aminated gelatin microspheres as a nasal delivery system for peptide drugs: evaluation of in vitro release and in vivo insulin absorption in rats. J Control Release 113: 31–7.

Wang SH, Fan Y, Makidon PE, et al. (2012a). Induction of immune tolerance in mice with a novel mucosal nanoemulsion adjuvant and self-antigen. Nanomedicine (Lond) 7:867–76.

Wang SH, Kirwan SM, Abraham SN, et al. (2012b). Stable dry powder formulation for nasal delivery of anthrax vaccine. J Pharm Sci 101: 31–47.

Wang X, Zheng C, Wu Z, et al. (2009). Chitosan-NAC nanoparticles as a vehicle for nasal absorption enhancement of insulin. J Biomed Mater Res B Appl Biomater 88:150–61.

Wearley LL. (1991). Recent progress in protein and peptide delivery by noninvasive routes. Crit Rev Ther Drug Carrier Syst 8:331–94.

Wen Z, Yan Z, He R, et al. (2011). Brain targeting and toxicity study of odorranalectin-conjugated nanoparticles following intranasal administration. Drug Deliv 18:555–61.

Witschi C, Mrsny RJ. (1999). In vitro evaluation of microparticles and polymer gels for use as nasal platforms for protein delivery. Pharm Res 16:382–90.

Wu H, Li J, Zhang Q, et al. (2012). A novel small Odorranalectin-bearing cubosomes: preparation, brain delivery and pharmacodynamic study on amyloid-beta(2)(5)(-)(3)(5)-treated rats following intranasal administration. Eur J Pharm Biopharm 80:368–78.

Xu W, Shen Y, Jiang Z, et al. (2004). Intranasal delivery of chitosan-DNA vaccine generates mucosal SIgA and anti-CVB3 protection. Vaccine 22:3603–12.

Yang ZZ, Zhang YQ, Wu K, et al. (2012). Tissue distribution and pharmacodynamics of rivastigmine after intranasal and intravenous administration in rats. Curr Alzheimer Res 9:315–25.

Zhang X, Wang Y, Zheng C, Li C. (2012). Phenylboronic acid-functionalized glycopolymeric nanoparticles for biomacromolecules delivery across nasal respiratory. Eur J Pharm Biopharm 82:76–84.