Nasal Drug Delivery Systems: An Overview

Muhammad U. Ghori, Mohammed H. Mahdi, Alan M. Smith, Barbara R. Conway[*]

Department of Pharmacy, University of Huddersfield, Huddersfield, UK
*Corresponding author: b.r.conway@hud.ac.uk

Abstract Since ancient times, drugs have been administered via the nasal route for therapeutic and recreational purposes. The interest in, and importance, of the systemic effects of drugs administered through the nasal route, have expanded over recent decades. Intra-nasal administration of drugs offers an interesting alternative for achieving systemic therapeutic effects of drugs that are comparable to the parenteral route, which can be inconvenient at times or oral administration, which can result in unacceptably low drug bioavailability. So, it is important to understand the potential and limitations of various nasal drug delivery systems. Therefore, the aim of this review article is to discuss the various pharmaceutical dosage forms that have the potential to be utilised for local or systemic drug administration. It is intuitively expected that this review will help to understand and further to develop suitable intra-nasal formulations to achieve specific therapeutic objectives.

Cite This Article: Muhammad U. Ghori, Mohammed H. Mahdi, Alan M. Smith, and Barbara R. Conway, "Nasal Drug Delivery Systems: An Overview." *American Journal of Pharmacological Sciences,* vol. 3, no. 5 (2015): 110-119. doi: 10.12691/ajps-3-5-2.

1. Introduction

Nasal drug delivery, which is in the focus of this review article, has received a significant attention in recent years as a convenient and reliable route, not only for local but also for the systemic administration of drugs [1,2,3]. The nasal cavity offers a number of distinctive advantages for systemic delivery such as [4,5,6]:

I- A large surface area for drug absorption.

II- Convenience and good patient compliance.

III- Rapid attainment of therapeutic drug levels in the blood.

IV- High drug permeability, especially for lipophilic and low molecular weight drugs.

V- Avoidance of harsh environmental and gastrointestinal conditions.

VI- Bypassing of hepatic first-pass metabolism.

VII- Potential direct drug delivery to the brain along the olfactory nerves.

VIII- Direct contact site for vaccines with lymphatic tissues.

The nasal cavity is an easily accessible route which is generally well tolerated [7]. The abundance of blood vessels in the nasal mucosa contributes to drug absorption, which is almost equal to intravenous injections in some instances [8]. The nasal route of drug delivery can be used for both local and systemic drug delivery [9]. For instance, localised nasal drug delivery is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions. A diverse range of drugs including corticosteroids, anti-histamines, anti-cholinergic and vasoconstrictors can be administered locally. In recent years, achieving a systemic drug action using the nose as the entry portal into the body has received more attention [10]. A wide range of pharmaceutical dosage forms including solutions, gels, suspensions, emulsions, liposomes and microparticles can be used to achieve systemic drug actions [11,12,13]. These dosage forms are mostly designed to exploit the advantage of a rapid onset of action when administered via nasal route. For example, morphine [14] and ketamine [15] can be delivered intra-nasally to achieve rapid analgesic effects. Moreover, vaccines can also be administered using the nose as a potential route, such as those for influenza [16].

2. Anatomy and physiology of nose

The nose is the primary entrance to the respiratory tract, allowing air to enter into the body for respiration [11]. The nasal cavity is 120-140 mm deep, runs from the nasal vestibule to the nasopharynx and is divided into two by a cartilaginous wall called nasal septum. The nose has a surface area of around 160 cm^2 and a total volume of ~16-19 ml [12]. The nose serves as the mean of bringing warm humidified air into the lungs. It is the primary organ for filtering out particles in the inspired air, and it also serves to provide a first-line immunologic defence as it brings the inspired air into contact with the mucous-coated membrane. The nose has three main regions: vestibular, turbinate and olfactory regions (Figure 1). The vestibular region is the anterior part of the nose and it is the narrowest part of the nasal cavity. The vibrissae cover most of this area which renders it capable of filtering out particles with an aerodynamic particle size larger than 10 µm that may be inhaled with air. In the vestibular region, the surface lining changes from skin, at the first part of the passage, to a stratified squamous epithelium [1,3]. The turbinate region is a large vascular part of the nose and

can be divided into superior, middle and inferior regions (Figure 1). It is lined with a pseudostratified columnar epithelium. It is composed of mucus secreting, ciliated, non-ciliated and basal cells (Figure 2). The ciliated and non-ciliated cells are covered with non-motile microvilli, which are responsible for increasing the surface area, thus, this is the region where the drug absorption is optimal. Ciliated cells are covered with approximately 100 motile cilia which are responsible for mucus transport so mucociliary clearance prevails. Once drug (as particles or in solution) find their way to the mucociliary area, they will be cleared from nasal cavity and then have limited access to the absorption site [17,18,19].
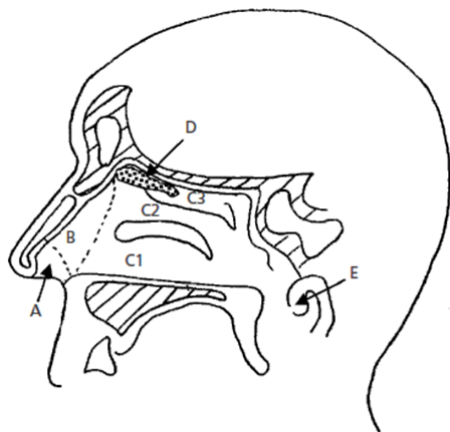
Figure 1. Sagittal section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E). Reproduced with permission from ref. [20]

The olfactory region is an area comprising about 8% of the total surface area of the nasal epithelium and is made of a non-ciliated, pseudostratified columnar epithelium. It is important for transporting drugs to the brain and cerebrospinal fluid (CSF). There is a mucus layer of 5 µm in thickness covering the epithelium cells which traps unwanted particles. The mucous secretion consists of mucin, water, salts,proteins such as albumin, immunoglobulin, lysozyme, and lactoferrin, and lipids [21]. The pH of the nasal secretions ranges from 5.0 to 6.5 [12,22].
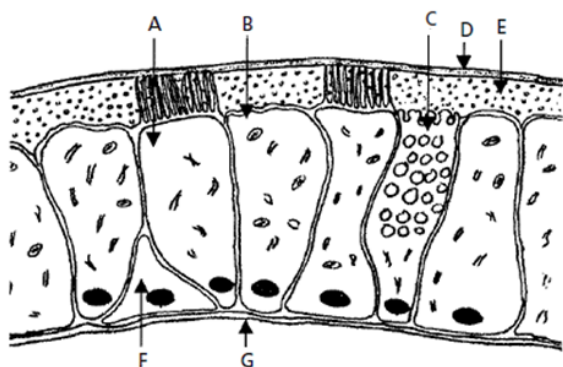

Figure 2. Cell types of the nasal epithelium with covering mucous layer showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), mucous gel-layer (D), sol layer (E), basal cells (F) and basement membrane (G). Reproduced with permission from ref. [20]

3. Biopharmaceutical Consideration

The easy accessibility and higher surface area makes the nose a potentially viable drug delivery organ. Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives. Therefore, before product development, important biopharmaceutical aspects need to be considered-firstly, whether it is intended for:

I-   Localised delivery
II- Systemic delivery
III- Single or repetitive administration

The feasibility of being able to achieve the therapeutic objectives will determine whether the development of a nasal delivery system is appropriate [5,7,10]. Comprehending the factors that can affect drug deposition, retention and absorption are essential to enable intelligent design of nasal formulations. Numerous physiological, anatomical, and pathological conditions must also be considered. Different types of nasal formulations available in the UK at the time of publication are enlisted in Table 1 [22]. However, a major challenge in designing nasal drug delivery formulations is to introduce the drug into a suitable vehicle system that provides drug stability and ideal dispensing characteristics. Elements such as selection of specific pharmaceutical excipients, delivery devices and processing methods need careful consideration. A schematic illustration of all the key parameters of a successful nasal formulation is shown in Figure 3.
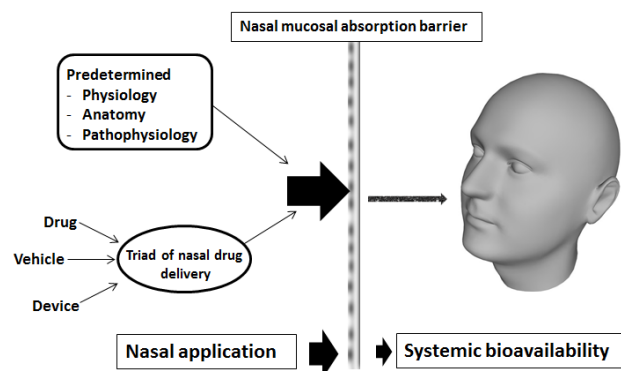
Figure 3. Consideration of formulation elements of nasal product development

4. Nose as a Drug Delivery Route: Advantages and Limitations

In addition to its benefits over parenteral routes in terms of convenience, the potential for delivering drugs directly into the brain along the olfactory nerves makes this route even more attractive [23]. The brain is a delicate organ with many vital functions and it is isolated and protected from the outside environment by several specific mechanisms. The blood-brain barrier (BBB), a tight tissue junction surrounding the brain, is one of such mechanisms resulting in a greater trans-endothelial electric resistance which hinders drug transport.

Table 1. Current formulations for nasal drug delivery [22]

Indication	Active pharmaceutical ingredient	Formulation
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder and diluent for reconstitution-aqueous spray Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Endometriosis Ovarian stimulation	Nafarelin acetate	Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone -dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Nocturia associated with multiple sclerosis The diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus. Establishing renal concentration capacity.	Desmopressin acetate	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

Table 2. Nasal drug absorption enhancers and mechanisms

Class of compound	Example	Possible action	Reference
Fatty acids	Dideconoylphosphatidylcholine, lysophosphatidylcholine	Membrane disruption	[24]
Surfactants	Sodium lauryl sulphate, saponin, polyoxyethylene-9-lauryl ether	Membrane disruption	[25-28]
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Open tight junctions, enzyme inhibition, mucolytic activity	[29-31]
Cyclodextrines and derivatives	α-, β-, γ-cyclodextrin DMβ-, HPβ-cyclodextrin	Open tight junctions, membrane disruption	[32,33]
Enzyme inhibitors	Bestatin, amastatia	Enzyme inhibition	[34]
Bio-adhesive materials	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions	[35]

In this context, over the last few years, an intra-nasal route has emerged as a promising approach for delivery of drugs to the brain. The delivery from the nose to the CNS may occur via the olfactory neuroepithelium and may involve paracellular, transcellular and/or neuronal transport [36] with this olfactory pathway presenting the potential to bypass the BBB [37]. The nasal route can also be a useful alternative to the oral route for drug absorption in situations where a use of the gastrointestinal route is unfeasible. Examples include: patients with nausea and vomiting; patients with swallowing difficulties children and geriatrics [38]. The rate and extent of absorption as well as plasma concentration vs time profiles are comparable with I.V. administration [39].

The foremost limitation on adoption of the nasal route is that it is not applicable to all drugs. The extent of drug absorption may depend on many physicochemical properties including acid-base dissociation constant (pK_a) and partition coefficient, molecular weight, particle size and solubility of the drug [11]. In general, for a drug to be absorbed it must be in solution and this can be problematic for drugs with low solubility. For instance, polar drugs and some macromolecules are not absorbed in sufficient concentrations because of poor membrane permeability, rapid clearance, and enzymatic degradation

within the nasal cavity [12]. The nasal mucosa is sensitive to local irritation by either drug or excipient [40]. Formulation factors such as the type of formulation (liquid, gel, and powder), excipient (solubilizer or absorption enhancer), drug concentration, pH and delivered volume also have a significant impact [41]. Physiological and anatomical factors include nasal blood flow, enzymatic degradation, mucociliary clearance and the physical condition of the nose; some conditions such as nasal atrophic rhinitis and severe vasomotor rhinitis can reduce the capacity of nasal drug absorption [38,39] and the drug can be lost by dripping out of the nose or down the back of the throat, thus reducing bioavailability [13]. Nasal mucociliary clearance can also reduce contact time and drug absorption by transporting the drug to the nasopharynx and then to the gastric intestinal tract [42]. Mucociliary clearance can be overcome by incorporating mucoadhesive polymers into the formulation, which may increase nasal absorption [43]. The mucus layer can also be a barrier for drug absorption either by limiting drug diffusion or by binding drugs to mucins. Some conditions such as the common cold and hay fever can also change the conditions within the nose, either by increasing or decreasing mucociliary clearance, or altering the permeability of the absorbing mucosa. These limitations must be recognised and addressed when designing formulations to target drug absorption by the nasal route [44,45,46,47].

5. Mechanism of Drug Absorption

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles easily pass through the mucus layer; however, large particles may find some difficulties [48]. Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer as a result of environmental or physiological changes [49]. Subsequent to a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers. Several mechanisms have been proposed, but paracellular and transcellular routes dominate [50].

Paracellular transport is slow and passive. There is an inverse correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was reported for drugs with a molecular weight greater than 1000 Daltons [48].

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions [50].

Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity.

5.1. Drug Absorption Enhancement

Many drugs having high water solubility have poor permeability across nasal epithelia and may present insufficient bioavailability. To enhance their permeation and bioavailability permeation enhancers are frequently employed [34]. In principle, permeation enhancers induce reversible modifications on the structure of the epithelial barrier. Although the exact mechanism of drug absorption/permeation enhancement is not well known, it is widely accepted that these materials modify the permeability of epithelial cell layer by modifying the phospholipid bilayer [35]. Different types of absorption/permeation enhancers are enlisted in Table 2 with their possible mechanism of action.

6. Nasal Drug Delivery Systems

6.1. Nasal Drops and Sprays

Nasal drops are one of the simplest and most convenient delivery systems among all formulations. The main limitation is the lack of precision in the administered dosage and the risk of contamination during use [51]. Nasal drops can be delivered with a pipette or by a squeezy bottle. These formulations are usually recommended for the treatment of local conditions, but challenges include microbial growth, mucociliary dysfunction and non-specific loss from the nose or down back the throat [13,41].

Nasal spray systems consist of a chamber, a piston and an operating actuator. Nasal sprays are comparatively more accurate than drops and generate precise doses (25 - 200 µl) per spray [41]. Several studies have shown that nasal sprays can produce consistent doses of reproducible plume geometry. Formulation properties such as thixotropy, surface tension and viscosity can potentially influence droplet size and dose accuracy [52,53,54,55]. Other factors such as the applied force, orifice size and design of the pump can also affect the droplet size which can impact the nasal deposition of sprays [10,13].

6.2. Nasal Gels

A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. The semi-solid characteristics of gels can be defined in terms of two dynamic mechanical properties: elastic modulus G' and viscous modulus G" [11]. The rheological properties of gels depend on the polymer type, concentration and physical state of the gel. They can range from viscous solutions (e.g. hypromellose, methylcellulose, xanthan gum and chitosan) to very hard, brittle gels (e.g. gellan gum, pectin and alginate). Bioadhesive polymers have shown good potential for nasal formulations and can control the rate and extent of drug release resulting in decreased frequency of drug administration and improved patient compliance [8,56]. Moreover, the prolonged contact time afforded at the site of absorption can improve drug bioavailability by slowing down mucociliary movement [57]. Gavini et al. (2011) observed improvements in the solubility of roxithromycin loaded into chitosan microspheres compared with the free drug when the intranasal drug absorption was assessed *in vivo* in rats [58]. The mechanism of mucoadhesion in the nasal

cavity can be explained by a number of theories, but it is generally accepted that the mechanism is based on two key stages, the contact and consolidation stages. So, when formulations containing bioadhesive polymers are instilled in the nasal cavity, they can spread over the nasal epithelium. Due to the increased surface contact, the polymer chains can diffuse within the mucus. This creates sufficient contact for entanglement. Secondary chemical bonds are then formed between the polymer chains and mucin molecules [13]. Various biocompatible and biodegradable polymers have been used to formulate mucoadhesive systems. These include poly-vinyl alcohol [59], chitosan [60], carbopol, alginate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch and gellan gum [13,61]. Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin [23], insulin [62], scopolamine hydrochloride [63], mometasone furoate [64], carvedilol [65], sumatriptan succinate [66], vaccines and proteins [67,68]. Ozsoy et al., 2000 [21] has investigated the formulation of ciprofloxacin hydrochloride using hydroxypropyl methylcellulose (HPMC) and the results suggested that the bioavailability of ciprofloxacin gel formulation prepared with HPMC was almost identical to the oral route [23].

In spite of most gels exhibiting shear-thinning behaviour (pseudoplasticity), some gel formulations with suitable rheological properties cannot be easily delivered using a normal nasal spray device. *In situ* gelation can be used to overcome this problem, [69] and has been investigated for the nasal delivery of mometasone furoate, carvedilol and influenza vaccine [66,67,68,69]. In such systems, the viscosity of the formulation must be low enough to allow dispensing from nasal spray device and viscous enough for adhesion on the application site.

In situ gel-forming polymeric formulations are drug delivery systems that are in solution form before administration in the body, but once administered, undergo *in situ* gelation, to form a gel. The formation of gels depends on factors like temperature modulation, pH change and presence of ions from which the drug gets released in a sustained and controlled manner. Fluid gels are potential alternative to *in situ* gels. These fluid gels are essentially structured liquids containing a gel forming polymer. They are prepared by applying a shear force to the polymer solution during the gelation process. This results in gelled particles suspended in an un-gelled polymer solution [70]. These can be formulated to behave as a viscoelastic liquid whilst maintaining a true gel microstructure within the gel particles. Recently, Mahdi et al., (2014) reported the development of a fluid gel formulation to achieve suitable viscoelastic properties to develop nasal sprays [13].

6.3. Nasal Suspensions and Emulsions

Suspensions are rarely used or investigated as nasal drug delivery systems. Analogous to marketed aqueous ophthalmic suspensions of the soft corticosteroid, loteprednol etabonate (e.g. Alrex®, Bausch and Lomb Pharmaceuticals), a nasal aqueous suspension of same drug containing microcrystalline sodium carboxymethylcellulose for stabilisation and retention in the nasal cavity was patented by Senju Pharmaceuticals

Inc., Osaka, Japan [71] and was intended for the local treatment of allergic rhinitis. Moreover, a nasal suspension for the delivery of insulin was investigated by Ando et al. (1998) [72]. Here, soybean-derived steryl glycoside and sterol mixtures (1%) were used as absorption enhancers and pharmacological bioavailabilities of 6.7% and 11.3% were achieved. However, for oral drug delivery it has been reported by several authors [73,74,75,76] that emulsions were superior to suspensions in enhancing the bioavailability of poorly soluble drugs and the trend is similar with nasal formulations. Absorption enhancement has been attributed to solubilisation of the drug and the lipophilic absorption enhancers in the composition. Similarly, other low solubility compounds have been formulated in emulsions to increase the drug solubility, e.g. diazepam [77] and testosterone [78].

Klang et al., 2015 [79] used a nano-suspension to target the brain through the nose. Formulation as a nanosuspension facilitated bypassing of the blood-brain barrier (BBB) for particles ranging between 1-500 nm. Moreover, recently researchers have also reported nasal administration of nano-emulsions for brain targeting [80,81,82].

6.4. Nasal Micellar and Liposomal Formulations

Different types of adjuvants can affect the drug absorption (described earlier, see section 5.1) and are often required to reach therapeutic plasma levels when hydrophilic macromolecular drugs such as peptides and proteins are delivered by the nasal route [83,84,85]. Among other surfactants used, bile salts are often used as enhancers, e.g. as micellar solutions. Tengamnuay and Mitra [86,87] described the use of micelles of sodium glycocholate and micelles thereof mixed with fatty acid (linoleic acid) as absorption enhancers for the model dipeptide (D-Arg2)-kyotorphin and for insulin in rats. The effect of mixed micelles was synergistic and superior compared to the single enhancer. Mixed micelles of sodium glycocholate and linoleic acid reduced the blood glucose level after nasal insulin administration to 47% of the glucose level after an identical nasal dosage of unenhanced insulin. Pure sodium glycocholate resulted in a reduction to 55%. Regarding the mechanism, in a difference to the membrane solubilizing effect of pure bile salts, the mixed micelles were proposed to have an effect on the nasal paracellular pathway. Hereby, the bile salts were considered to act as solubilizing agents for the fatty acids thus making them more available at the nasal mucosa [86]. The absorption modifying effect of mixed micelles was reversible after 20-40 min and the morphological alterations of the nasal mucosa were only mild to moderate after 5 h of exposure [86,87]. However, measurement of marker enzymes in rat nasal perfusate showed that the damaging effect of mixed micelles on the epithelial membrane is significantly greater compared with pure sodium glycocholate solution and phosphate buffered saline after 90 min exposure [88].

Liposomes have also been investigated as nasal drug delivery systems and absorption enhancing effects were found for insulin and calcitonin *in vitro* permeability studies [89]. The enhancement effect was attributed to increased nasal retention of peptides. The best carrier

effect for calcitonin was demonstrated with cationic liposomes as they were found to adhere intimately to the nasal mucosal surface, facilitating the penetration of the encapsulated drug [89]. Similar observations were made for desmopressin-loaded cationic liposomes which resulted in enhanced antidiuretic effects in rats compared with anionic liposomes and solutions [90]. Muramatsu et al. (1999) [91] showed increased nasal absorption of insulin for liposomes of high membrane fluidity compared to more rigid particles. However, the absorption enhancing effect of liposomes is difficult to separate from the enhancing effects of the single components such as phosphatidylcholines and steryl glycosides. Moreover, proliposomes have also shown potential in nasal drug delivery. Proliposomes are dry, free-flowing granules composed of sorbitol as carrier and lipids that form a liposomal dispersion on contact with water. Their advantages are the combination of a fast onset (surface drug) and prolonged drug action (encapsulated drug) as demonstrated for propranolol and nicotine [92,93].

6.5. Nasal Powders

Particulate nasal dosage forms are usually prepared by simply mixing the drug substance and the excipients [94,95], by spray-drying or freeze- drying of drug [96,97,98,99,100]. Dry-powder formulations containing bioadhesive polymers for the nasal delivery of peptides and proteins was first investigated by Nagai et al. (1984) [101]. Water-insoluble cellulose derivatives and Carbopol® 934P were mixed with insulin and the powder mixture was administered nasally. The powder took up water, swelled, and established a gel with a prolonged residence time in the nasal cavity. Glucose reduction was one-third of that achieved using an i.v. injection of the same insulin dose. Powder formulations for nasal drug delivery have since been widely investigated, e.g. for a somatostatin analogue using cross-linked dextran and microcrystalline cellulose [102], for glucagon using microcrystalline cellulose [103], for leuprolide and calcitonin using microcrystalline cellulose in combination with hydroxypropyl cellulose [104], and for gentamicin sulfate using hydroxypropyl methylcellulose [99]. A bioadhesive powder containing beclomethasone dipropionate for local treatment of allergic rhinitis and hydroxypropyl cellulose as the carrier had a significantly enhanced nasal residence time compared with administration of a solution as drops [105]. Ugwoke et al. (2000) [97] compared the nasal retention time of apomorphine, freeze-dried with lactose, Carbopol® 971P or sodium carboxymethylcellulose. Three hours post insufflation, 58%, 12%, and 27%, respectively, of the formulation, had been cleared from the nasal cavity. In all cases, the administered powder reduced the nasal mucociliary clearance. The difference in nasal residence time led to a sustained plasma peak level from the Carbopol® formulation of 52 min vs. 11 min for the lactose powder while maintaining similar bioavailabilities [105]. Callens and Remon (2000) [98] demonstrated nasal insulin delivery with freeze-dried powders of waxy maize starch and Carbopol® 974P, reaching an absolute bioavailability of 14.4%. Comparison of different starch / Carbopol® 974P and maltodextrin / Carbopol® 974P mixtures by oscillatory rheology showed no synergistic increase in the viscosity and elasticity when combined with mucus, which is often used as an indicator of bioadhesion [106]. However, the formulation with the highest bioavailability had the highest storage modulus, i.e. the most solid-like properties. It was also observed that the insulin bioavailability was markedly reduced after repeated administration of the powder formulations [107]. Although the reasons remained unclear, it was speculated that the powders were not completely cleared from the nasal cavity after each delivery but formed a physical barrier on the nasal mucosa inhibiting penetration of the drug on subsequent administrations. Thus, bioadhesion seemed to have reversed into deteriorating the bioavailability. Also inorganic, water-insoluble powder formulations such as calcium phosphates enhanced the drug absorption in rats after nasal administration [95], although they did not promote the *in vitro* drug permeability across rabbit nasal mucosa [108]. Retardation at the site of administration was proposed as a possible explanation.

6.6. Nasal Microparticles

Using microparticles as another way of prolonging the residence time in the nasal cavity was introduced in 1987 [109]. It was proposed that microspheres of albumin, starch, and DEAE-dextran (diethyl aminoethyl-dextran) absorbed water and formed a gel-like layer which was cleared slowly from the nasal cavity. Three hours after administration, 50% of the delivered amount of albumin and starch microspheres and 60% of the dextran microspheres were still present at the site of deposition. It was suggested that an increased contact time could increase the absorption efficiency of drugs. As proposed, the relative intranasal bioavailability (v.s. subcutaneous) of human growth hormone in sheep was increased from 0.1% for the solution to 2.7% for the degradable starch microsphere formulation. The addition of absorption enhancer, lysophosphatidylcholine, further enhanced growth hormone absorption as a relative bioavailability of 14.4% was achieved [110]. Björk and Edman (1990) [111] showed that plasma glucose reduction after nasal insulin administration was comparable for degradable starch microspheres (cross-linked with epichlorohydrin) and insoluble starch powder (molecular weight 25 kDa) but significantly lower for soluble starch powder (molecular weight 11 kDa). It was therefore concluded that crucial parameters for the absorption promoting effect of microspheres are water absorption and aqueous insolubility. No alteration of the nasal mucosa was observable by scanning electron microscopy after 8 weeks of twice daily administration of starch microspheres, except slight hyperplasia in the septum wall [112]. Although DEAE-dextran microspheres were retained strongly in the nasal cavity [109], they were not successful in promoting nasal insulin absorption in rats [113]. The insulin was too tightly bound to the DEAE-groups to be released by a solution with an ionic strength corresponding to physiological conditions. Dextran microparticles without ion exchange groups induced a 25% decrease in blood glucose level about 40 min after administration compared with initial levels. In a later study, dextran microspheres with a different distribution of the encapsulated insulin were compared [114]. When

insulin was situated on the microsphere surface, a 52% reduction in plasma glucose was induced 30 min after administration in rats. However, microspheres, which included the insulin in the spherical matrix, reached a maximum plasma glucose level reduction of 30% after 60 min. Possibly, the limited amount of fluid in the nasal cavity is responsible for the observed differences, as the microspheres must be completely swollen to release the entire amount of incorporated insulin [115].

Chitosan also has potential as an excipient in microparticulate drug delivery systems. *In vivo* studies in sheep showed a half-life of nasal clearance for chitosan microparticles of 115 min compared with 43 min for a solution of the polymer [116]. In general, chitosan formulations, whether in the form of microparticles or powders, were shown to provide a better absorption enhancing effect than chitosan solutions [117,118]. Moreover, recently solid lipid nanoparticles have also shown promising results [119,120] and were shown to increase the brain targeting of rosmarinic acid following nasal delivery for potential management of Huntington's disease [121].

7. Conclusions

Over last decade, the nasal cavity has become one the promising and potentially versatile route for delivering drugs. In particular, its unique capability of extending the drug release, by passing the hepatic first-pass metabolism and direct delivery of drugs to brain holds great promise in the field of drug delivery. A growing body of evidence relating to nasal drug delivery suggest it might the used for challenging drugs which can facilitate the pharmaceutical manufacturing and drug delivery challenges. Various pharmaceutical dosage forms and their potential to be utilised for local or systemic drug administration has been discussed in their review article. It is intuitively expected that this review will help to understand and further to develop the intra-nasal formulations to achieve specific therapeutic objectives. However, a number of technical and practical issues, which are also highlighted in this review article, remain a hurdle to be overcome in order for the full potential to be realised.

Acknowledgement

References

[1]   CHIEN, Y.W., & CHANG, S.F., (1987). Intranasal drug delivery for systemic medications. Critical Reviews In Therapeutic Drug Carrier Systems. 4 (2), 67-194.

[2]   HARRIS, A.S., (1993). Review: Clinical opportunities provided by the nasal administration of peptides. Journal of Drug Targeting 1, 101-116.

[3]   CHIEN, Y.W., SU, K.S.E., & CHANG, S.F., (1989), Anatomy and physiology of the nose, in Y. W. Chen, K. S. E. Su, and S.-F. Chang, eds., Nasal systemic drug delivery: Drugs and the Pharmaceutical Sciences, v. 39: New York, Marcel Dekker Inc, p. 1-19.

[4]   DUQUESNOY, C., MAMET, J.P., SUMNER, D., & FUSEAU, E., (1998). Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. European Journal of Pharmaceutical Sciences 6, 99-104.

[5]   ELLER, N., KOLLENZ, C.J., BAUER, P., & HITZENBERGER, G., (1998). The duration of antidiuretic response of two desmopressin nasal sprays. International Journal of Clinical Pharmacology and Therapeutics. 36 (9), 494-500.

[6]   SLOT, W.B., MERKUS, F.W.H.M., DEVENTER, S.J.H.V., & TYTGAT, G.N.J., (1997). Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. Gastroenterology. 113, 430-433.

[7]   KNOESTER, P.D., JONKER, D.M., HOEVEN, R.T.M.V.D., VERMEIJ, T.A.C., EDELBROEK, P.M., BREKELMANS, G.J., & HAAN, G.J.D., (2002). Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. British Journal of Clinical Pharmacology. 53, 501-507.

[8]   RATHBONE, M. J., HADGRAFT, J., & ROBERTS, M. S. (Eds.). (2002). Modified-release drug delivery technology. CRC Press.

[9]   CASETTARI, L & ILLUM. L (2014), Chitosan in nasal delivery systems for therapeutic drugs, Journal of Controlled Release. 190, 189-200.

[10] KUBLIK, H., & VIDGREN, M. T., (1998). Nasal delivery systems and their effect on deposition and absorption. Advanced Drug Delivery Reviews, 29, 157-177.

[11] CHATURVEDI, M., KUMAR. M., & PATHAK. K., (2011). A review on mucoadhesive polymer used in nasal drug delivery system. Journal of Advanced Pharmaceutical Technology and Research, 4, 215-222.

[12] AULTON, M. E., TAYLOR, K., (2013). Aulton's Pharmaceutics: the design and manufacture of medicines, Edinburgh, Churchill Livingstone.

[13] MAHDI, M. H., CONWAY, B. R., & SMITH, A. M. (2015). Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 488(1), 12-19.

[14] RHIDIAN, R., & GREATOREX, B., (2015). Chest pain in the recovery room, following topical intranasal cocaine solution use. British Medical Journal Case Reports doi: 10.1136/bcr-2015-20969

[15] ANDRADE, C., (2015). Intranasal drug delivery in neuropsychiatry: Focus on intranasal ketamine for refractory depression. Journal of Clinical Psychiatry 76(5): 628-631.

[16] HERMANN, N., (2015). Effectiveness of live attenuated influenza vaccines and trivalent inactivated influenza vaccines against confirmed influenza in children and adolescents in Saxony-Anhalt, 2012/13. Gesundheitswesen 77(7): 499-501

[17] SINGH, L., & KHAN, A. D., Nasal drug delivery: a promising way for brain targeting. The Pharma Research 13.2, 1-12.

[18] PRAJAPATI, S. T., Pathak, S.P., Thakkar, J. H., & Patel, C. N., (2015). Nanoemulsion based intranasal delivery of risperidone for nose to brain targeting. Bulletin of Pharmaceutical Research 5, 6-13.

[19] MUNDLIA, J., & MUKESH, K. (2015). Nasal drug delivery: An overview. International Journal of Pharmaceutical Sciences and Research 6, 951-956.

[20] UGWOKE, M. I., VERBEKE, N., & KINGET, R. (2001). The biopharmaceutical aspects of nasal mucoadhesive drug delivery. Journal of Pharmacy and Pharmacology, 53(1), 3-22.

[21] OZSOY, Y., TUNCEL, T., CAN, A., AKEV, N., BIRTEKSOZ, S. & GERCEKER, A. (2000). *In vivo* studies on nasal preparations of ciprofloxacin hydrochloride. Pharmazie, 55, 607-609

[22] Electronic Medicines Compendium (2015) [Database on the Internet]. Datapharm Communications Ltd. http://emc.medicines.org.uk.

[23] UGWOKE, M. I., AGU, R. U., VERBEKE, N., & KINGET, R. (2005). Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Advanced Drug Delivery Reviews, 57(11), 1640-1665.

[24] MERKUS, F. W. H. M., SCHIPPER, N. G. M., HERMENS, W. A. J. J., ROMEIJN, S. G., & VERHOEF, J. C. (1993). Absorption enhancers in nasal drug delivery: efficacy and safety. Journal of Controlled Release, 24(1), 201-208.

[25] NATSUME, H., IWATA, S., MIYAMOTO, M., KAWAI, T., SUGIBAYASHI, K., MORIMOTO, Y., 1996. Screening of absorption enchancers for nasal peptide and protein delivery.

Proceed. Internat. Symp. Control Release Bioactive Materials. 23, 481-482.

[26] ZHOU, M., DONOVAN, M.D., 1996. Recovery of the nasal mucosa following laureth-9 induced damage. International Journal of Pharmaceutics.130, 93-102.

[27] CHANDLER, S.G., ILLUM, L., THOMAS, N.W., 1991. Nasal absorption in rats. II. Effect of enhancers on insulin absorption and nasal histology. International Journal Pharmaceutics. 76, 61-70.

[28] CHANDLER, S.G., ILLUM, L., THOMAS, N.W., 1994. Nasal absorption in rats. III. Effect on lysophospholipids on insulin absorption and nasal histology. Pharmaceutical Research. 11 (11), 1623-1630.

[29] YAMAMOTO, A., MORITA, T., HASHIDA, M., SEZAKI, H., 1993. Effect of absorption promoters on nasal absorption of drugs with various molecular weights. International Journal of Pharmaceutics. 93, 91-99.

[30] AUNGST, B.J., ROGERS, N.J., SHEFFER, E., 1988. Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promotor. Journal of Pharmacology and Experimental Therapeutics. 244, 23-27.

[31] BAGGER, M.A., NIELSEN, H.W., BECHGAARD, E., 2001. Nasal bioavailability of peptide T in rabbits: absorption enhancement by sodium glycolate and glycofurol. European Journal of Pharmaceutical Sciences. 14, 69-74.

[32] MARTTIN, E., VERHOEF, J.C., MERKUS, F.W.H.M., 1998. Efficacy, safety and mechanism of cyclodextrins as absorption enhancers in nasal drug delivery of peptide and protein drugs. Journal of Drug Targeting. 6 (1), 17-36.

[33] MATSUBARA, K., ABE, K., IRIE, T., UEKAMA, K., 1995. Improvement of nasal bioavailability of luteinizing hormone-releasing hormon agonist, buserelin, by cyclodextrin derivatives in rats. Journal of Pharmaceutical Sciences. 84 (11), 1295-1300.

[34] TOUITOU, E., & BARRY, B. W. (Eds.). (2006). Enhancement in drug delivery. CRC Press.

[35] DAVIS, S. S., & ILLUM, L. (2003). Absorption enhancers for nasal drug delivery. Clinical Pharmacokinetics, 42(13), 1107-1128.

[36] VYAS, T. K., SHAHIWALA, A., MARATHE, S., & MISRA, A. (2005). Intranasal drug delivery for brain targeting. Current drug delivery, 2(2), 165-175.

[37] HANSON, L. R., & FREY, W. H. (2008). Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease. British Medical Journal Neuroscience, 9 (Suppl 3), S5.

[38] BEHL, C. R., PIMPLASKAR, H. K., SILENO, A. P., DEMEIRELES, J. & ROMEO, V. D. (1998). Effects of physicochemical properties and other factors on systemic nasal drug delivery. Advanced Drug Delivery Reviews, 29, 89-116.

[39] SINGH, A. K., SINGH, A. & MADHV, N. V., (2012). Nasal cavity, a promising transmucosal platform for drug delivery and research approaches from nasal to brain targeting. Journal of Drug Delivery and Therapeutics. 2(3), 22-33.

[40] HARRIS, A. S., (1993). Review: clinical opportunities provided by the nasal administration of peptides. Journal of Drug Targeting, 1, 101-116.

[41] HUSSEIN, N. R., (2014). Bioadhesive microparticles and liposomes of anti-Parkinson drugs for nasal delivery. PhD thesis, University of Central Lancashire.

[42] JADHAV, K. R., GAMBHIRE, M. N., SHAIKH, I. M., KADAM, V. J., & PISAL, S. S. (2007). Nasal drug delivery system-factors affecting and applications. Current Drug Therapy, 2(1), 27-38.

[43] SUMAN, J. D. (2003). Nasal drug delivery. Expert Opinion on Biological Therapy, 3(3), 519-523.

[44] ALAGUSUNDARAM, M., CHENGAIAH, B., GNANAPRAKASH, K., RAMKANTH, S., CHETTY, C. M., & DHACHINAMOORTHI, D. (2010). Nasal drug delivery system-an overview. International Journal of Research and Pharmaceutical Sciences, 1(4), 454-465.

[45] SINTOV, A. C., LEVY, H. V., & BOTNER, S. (2010). Systemic delivery of insulin *via* the nasal route using a new microemulsion system: *in vitro* and *in vivo* studies. Journal of Controlled Release, 148(2), 168-176.

[46] UPADHYAY, S., PARIKH, A., JOSHI, P., UPADHYAY, U. M., & CHOTAI, N. P. (2011). Intranasal drug delivery system-A glimpse to become maestro. Journal of Applied Pharmaceutical Science, 1(03), 34-44.

[47] KARLA, P. K., KWATRA, D., GAUDANA, R., & MITRA, A. K. (2008). Nasal drug delivery; Modified-release drug delivery technology. 2nd ed. London, UK: Informa Healthcare.

[48] HUANG, C. H., KIMURA, R., NASSAR, R. B., & HUSSAIN, A. (1985). Mechanism of nasal absorption of drugs I: Physicochemical parameters influencing the rate of in situ nasal absorption of drugs in rats. Journal of pharmaceutical sciences,74(6), 608-611.

[49] SHINICHIRO, H., TAKATSUKA, Y., & HIROYUKI, M. (1981). Mechanisms for the enhancement of the nasal absorption of insulin by surfactants. International Journal of Pharmaceutics, 9(2), 173-184.

[50] DUVVURI, S., MAJUMDAR, S., & MITRA, A. K. (2003). Drug delivery to the retina: challenges and opportunities. Expert opinion on biological therapy, 3(1), 45-56.

[51] WASHINGTON, N., WASHINGTON, C., WILSON, C.G., (2001). Physiological pharmaceutics: barriers to drug absorption. Taylor & Francis, New York.

[52] DJUPESLAND, P.G. (2013). Nasal drug delivery devices: characteristics and performance in a clinical perspective-a review. Drug Delivery and Translational Research 3, 42–62.

[53] HANSEN, K., KIM, G., DESAI, K. G. H., PATEL, H., OLSEN, K. F., CURTIS-FISK, J., & SCHWENDEMAN, S. P. (2015). Feasibility investigation of cellulose polymers for mucoadhesive nasal drug delivery applications. Molecular Pharmaceutics, 12(8), 2732-2741.

[54] RASSU, G., SODDU, E., COSSU, M., BRUNDU, A., CERRI, G., MARCHETTI, N., & DALPIAZ, A. (2015). Solid microparticles based on chitosan or methyl-β-cyclodextrin: A first formulative approach to increase the nose-to-brain transport of deferoxamine mesylate. Journal of Controlled Release, 201, 68-77.

[55] MENAKA, M., & PANDEY, V. P. Formulation development and evaluation of cinnarizine nasal spray. Pharma Health Sciences, 2(4), 339-346.

[56] NAKAMURA, K., TANAKA, Y., & SAKURAI, M. (1996) Dynamic mechanical properties of aqueous gellan solutions in the sol–gel transition region Carbohydrate Polymers, 30. 101–108.

[57] PATIL, S. B., & SAWANT, K. K. (2008). Mucoadhesive microspheres: a promising tool in drug delivery. Current drug delivery, 5(4), 312-318.

[58] GAVINI, E., RASSU, G., FERRARO, L., GENEROSI, A., RAU, J. V., BRUNETTI, A., & DALPIAZ, A. (2011). Influence of chitosan glutamate on the *in vivo* intranasal absorption of rokitamycin from microspheres. Journal of Pharmaceutical Sciences, 100(4), 1488-1502.

[59] SWAMY, N. G. N., & ABBAS, Z. (2012). Preparation and *in vitro* characterization of mucoadhesive polyvinyl alcohol microspheres containing amlodipine besylate for nasal administration. Indian Journal of Pharmaceutical Education and Research, 46(1), 55.

[60] CASETTARI, L., & ILLUM, L. (2014). Chitosan in nasal delivery systems for therapeutic drugs. Journal of Controlled Release, 190, 189-200.

[61] RATHANANAND, M., KUMAR, D. S., SHIRWAIKAR, A., KUMAR, R., SAMPATH KUMAR, D., & PRASAD, R. S. (2007). Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Indian Journal of Pharmaceutical Sciences, 69(5), 651.

[62] DYER, A. M., WATTS, P., CASTILE, J., JABBAL-GILL, I., NANKERVIS, R., SMITH, A., ILLUM. L. (2002). Nasal delivery of insulin using novel chitosan based formulations: a comparative study in two animal models between simple chitosan formulations and chitosan nanoparticles. Pharmaceutical Research. 19, 998-1008.

[63] CAO, S. L., ZHANG, Q. Z., & JIANG, X. G. (2007). Preparation of ion-activated *in situ* gel systems of scopolamine hydrobromide and evaluation of its antimotion sickness efficacy. Acta Pharmacological Sinica, 28(4), 584-590.

[64] ZITT, M., KOSOGLOU, T., & HUBBELL, J. (2007). Mometasone furoate nasal spray. Drug Safety, 30(4), 317-326.

[65] NILESH, S. (2013). Nanosuspension based in situ gelling nasal spray of carvedilol: development, *in vitro* and *in vivo* characterization. AAPS PharmSciTech 14(1): 189-199

[66] GALGATTE, U. C., KUMBHAR, A. B., & CHAUDHARI, P. D. (2014). Development of in situ gel for nasal delivery: design, optimization, *in vitro* and i*n vivo* evaluation. Drug Delivery, 21(1), 62-73.

[67] VILA, A., SANCHEZ, A., TOBIO, M., CALVO, P., & ALONSO, M. J. (2002). Design of biodegradable particles for protein delivery. Journal of Controlled Release, 78(1), 15-24.

[68] DAVIS, S. S. (2001). Nasal vaccines. Advanced Drug Delivery Reviews, 51(1), 21-42.

[69] MADAN, M., LEWIS, M. B., UDUPA, S., BAIG, N. (2009). In situ forming polymeric drug delivery systems. Indian Journal Pharmaceutical Sciences, 71, 242-51.

[70] SWORN, G., SANDERSON, G. R., & GIBSON, W. (1995). Gellan gum fluid gels. Food Hydrocolloids, 9(4), 265-271.

[71] DOI, K. (2002). U.S. Patent No. 6,368,616. Washington, DC: U.S. Patent and Trademark Office.

[72] ANDO, T., MAITANI, Y., YAMAMOTO, T., TAKAYAMA, K., & NAGAI, T. (1998). Nasal insulin delivery in rabbits using soybean-derived sterylglucoside and sterol mixtures as novel enhancers in suspension dosage forms. Biological and Pharmaceutical Bulletin, 21(8), 862-865.

[73] AIKAWA, K., MATSUMOTO, K., UDA, H., TANAKA, S., SHIMAMURA, H., ARAMAKI, Y., & TSUCHIYA, S. (1998). Prolonged release of drug from o/w emulsion and residence in rat nasal cavity. Pharmaceutical Development & Technology, 3(4), 461-469.

[74] TAMILVANAN, S. (2008). Oil-in-Water nanosized emulsions: Medical Applications. Pharmaceutical Sciences Encyclopedia. John Wiley & Sons, Inc.

[75] KARARLI, T. T., NEEDHAM, T. E., GRIFFIN, M., SCHOENHARD, G., FERRO, L. J., & ALCORN, L. (1992). Oral delivery of a renin inhibitor compound using emulsion formulations. Pharmaceutical Research, 9(7), 888-893.

[76] Kararli, T. T., Needham, T. E., Schoenhard, G., Baron, D. A., Schmidt, R. E., Katz, B., & Belonio, B. (1992). Enhancement of nasal delivery of a renin inhibitor in the rat using emulsion formulations. Pharmaceutical Research, 9(8), 1024-1028.

[77] LI, L., NANDI, I., & KIM, K. H. (2002). Development of an ethyl laurate-based microemulsion for rapid-onset intranasal delivery of diazepam. International Journal of Pharmaceutics, 237(1), 77-85.

[78] KO, K. T., NEEDHAM, T. E., & ZIA, H. (1998). Emulsion formulations of testosterone for nasal administration. Journal of Microencapsulation, 15(2), 197-205.

[79] KLANG, V., SCHWARZ, J. C., & VALENTA, C. (2015). Nanoemulsions in Dermal Drug Delivery. In Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement (pp. 255-266). Springer Berlin Heidelberg.

[80] ZHANG, X., & WU, B. (2015). Submicron lipid emulsions: a versatile platform for drug delivery. Current Drug Metabolism, 16(3), 211-220.

[81] SHINDE, R. L., BHARKAD, G. P., & DEVARAJAN, P. V. (2015). Intranasal microemulsion for targeted nose to brain delivery in neurocysticercosis: role of docosahexaenoic acid. European Journal of Pharmaceutics and Biopharmaceutics, 96, 363-379.

[82] YADAV, S., GATTACCECA, F., PANICUCCI, R., & AMIJI, M. M. (2015). Comparative biodistribution and pharmacokinetic analysis of cyclosporine-a in the brain upon intranasal or intravenous administration in an oil-in-water nanoemulsion formulation. Molecular Pharmaceutics, 12(5), 1523-1533.

[83] DE PONTI, R., & LARDINI, E. (1991). Use of chemical enhancers for nasal drug delivery. Drug Development & Industrial Pharmacy, 17(11), 1419-1436.

[84] MERKUS, F. W. H. M., SCHIPPER, N. G. M., HERMENS, W. A. J. J., ROMEIJN, S. G., & VERHOEF, J. C. (1993). Absorption enhancers in nasal drug delivery: efficacy and safety. Journal of Controlled Release, 24(1), 201-208.

[85] NATSUME, H., IWATA, S., OHTAKE, K., MIYAMOTO, M., YAMAGUCHI, M., HOSOYA, K. I & MORIMOTO, Y. (1999). Screening of cationic compounds as an absorption enhancer for nasal drug delivery. International Journal of Pharmaceutics, 185(1), 1-12.

[86] TENGAMNUAY, P., & MITRA, A. K. (1990). Bile salt–fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength, adjuvant composition, and lipid structure on the nasal absorption of [D-Arg2] kyotorphin. Pharmaceutical Research, 7(2), 127-133.

[87] TENGAMNUAY, P., & MITRA, A. K. (1990). Bile salt–fatty acid mixed micelles as nasal absorption promoters of peptides. II. *In vivo* nasal absorption of insulin in rats and effects of mixed micelles on the morphological integrity of the nasal mucosa. Pharmaceutical Research, 7(4), 370-375.

[88] SHAO, Z., & MITRA, A. K. (1994). Bile salt–fatty acid mixed micelles as nasal absorption promoters. III. Effects on nasal transport and enzymatic degradation of acyclovir prodrugs. Pharmaceutical Research, 11(2), 243-250.

[89] LAW, S. L., & SHIH, C. L. (2001). Characterization of calcitonin-containing liposome formulations for intranasal delivery. Journal of Microencapsulation, 18(2), 211-221.

[90] LAW, S. L., HUANG, K. J., & CHOU, H. Y. (2001). Preparation of desmopressin-containing liposomes for intranasal delivery. Journal of Controlled Release, 70(3), 375-382.

[91] 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 Development & Industrial Pharmacy, 25(10), 1099-1105.

[92] JUNG, B. H., CHUNG, B. C., CHUNG, S. J., LEE, M. H., & SHIM, C. K. (2000). Prolonged delivery of nicotine in rats via nasal administration of proliposomes. Journal of Controlled Release, 66(1), 73-79.

[93] JUNG, B. H., CHUNG, S. J., & SHIM, C. K. (2002). Proliposomes as prolonged intranasal drug delivery systems. STP Pharma sciences, 12(1), 33-38.

[94] TAKENAGA, M., SERIZAWA, Y., AZECHI, Y., OCHIAI, A., KOSAKA, Y., IGARASHI, R., & MIZUSHIMA, Y. (1998). Microparticle resins as a potential nasal drug delivery system for insulin. Journal of Controlled Release, 52(1), 81-87.

[95] ISHIKAWA, E., YANAKA, K., SUGIMOTO, K., AYUZAWA, S., & NOSE, T. (2002). Reversible dementia in patients with chronic subdural hematomas. Journal of Neurosurgery, 96(4), 680-683.

[96] ILLUM, L., FARRAJ, N. F., & DAVIS, S. S. (1994). Chitosan as a novel nasal delivery system for peptide drugs. Pharmaceutical Research, 11(8), 1186-1189.

[97] UGWOKE, M. I., AGU, R. U., VANBILLOEN, H., BAETENS, J., AUGUSTIJNS, P., VERBEKE, N., & BORMANS, G. (2000). Scintigraphic evaluation in rabbits of nasal drug delivery systems based on carbopol 971P® and carboxymethylcellulose. Journal of Controlled Release, 68(2), 207-214.

[98] CALLENS, C., & REMON, J. P. (2000). Evaluation of starch–maltodextrin-Carbopol® 974 P mixtures for the nasal delivery of insulin in rabbits. Journal of Controlled Release, 66(2), 215-220.

[99] HASÇIÇEK, C., GÖNÜL, N., & ERK, N. (2003). Mucoadhesive microspheres containing gentamicin sulfate for nasal administration: preparation and *in vitro* characterization. Il Farmaco, 58(1), 11-16.

[100] FERNANDEZ-URRUSUNO, R., CALVO, P., REMUÑÁN-LÓPEZ, C., VILA-JATO, J. L., & ALONSO, M. J. (1999). Enhancement of nasal absorption of insulin using chitosan nanoparticles. Pharmaceutical Research, 16(10), 1576-1581.

[101] NAGAI, K., & THØGERSEN, H. C. (1984). Generation of β-globin by sequence-specific proteolysis of a hybrid protein produced in *Escherichia coli*. Nature. 309(5971), 810-812

[102] OECHSLEIN, C. R., FRICKER, G., & KISSEL, T. (1996). Nasal delivery of octreotide: Absorption enhancement by particulate carrier systems. International Journal of Pharmaceutics, 139(1), 25-32.

[103] TESHIMA, D., YAMAUCHI, A., MAKINO, K., KATAOKA, Y., ARITA, Y., NAWATA, H., & OISHI, R. (2002). Nasal glucagon delivery using microcrystalline cellulose in healthy volunteers. International Journal of Pharmaceutics, 233(1), 61-66.

[104] SUZUKI, Y., & MAKINO, Y. (1999). Mucosal drug delivery using cellulose derivatives as a functional polymer. Journal of Controlled Release, 62(1), 101-107.

[105] UGWOKE, M. I., SAM, E., VAN DEN MOOTER, G., VERBEKE, N., & KINGET, R. (1999). Nasal mucoadhesive delivery systems of the anti-parkinsonian drug, apomorphine: influence of drug-loading on *in vitro* and *in vivo* release in rabbits. International Journal of Pharmaceutics, 181(1), 125-138.

[106] CALLENS, C., CEULEMANS, J., LUDWIG, A., FOREMAN, P., & REMON, J. P. (2003). Rheological study on mucoadhesivity of some nasal powder formulations. European Journal of Pharmaceutics and Biopharmaceutics, 55(3), 323-328.

[107] CALLENS, C., PRINGELS, E., & REMON, J. P. (2003). Influence of multiple nasal administrations of bioadhesive powders on the insulin bioavailability. International Journal of Pharmaceutics, 250(2), 415-422.

[108] ISHIKAWA, F., KATSURA, M., TAMAI, I., & TSUJI, A. (2001). Improved nasal bioavailability of elcatonin by insoluble powder

formulation. International Journal of Pharmaceutics, 224(1), 105-114.

[109] ILLUM, L. H. H. O. N., JØRGENSEN, H., BISGAARD, H., KROGSGAARD, O., & ROSSING, N. (1987). Bioadhesive microspheres as a potential nasal drug delivery system. International Journal of Pharmaceutics, 39(3), 189-199.

[110] ILLUM, L., FARRAJ, N. F., DAVIS, S. S., JOHANSEN, B. R., & O'HAGAN, D. T. (1990). Investigation of the nasal absorption of biosynthetic human growth hormone in sheep-use of a bioadhesive microsphere delivery system. International Journal of Pharmaceutics, 63(3), 207-211.

[111] BJÖRK, E., & EDMAN, P. (1990). Characterization of degradable starch microspheres as a nasal delivery system for drugs. International Journal of Pharmaceutics, 62(2), 187-192.

[112] EDMAN, P., BJÖRK, E., & RYDEN, L. (1992). Microspheres as a nasal delivery system for peptide drugs. Journal of Controlled Release, 21(1), 165-172.

[113] RYDEN, L., & EDMAN, P. (1992). Effect of polymers and microspheres on the nasal absorption of insulin in rats. International Journal of Pharmaceutics, 83(1), 1-10.

[114] PERESWETOFF-MORATH, L., & EDMAN, P. (1995). Dextran microspheres as a potential nasal drug delivery system for insulin-*in vitro* and *in vivo* properties. International journal of pharmaceutics, 124(1), 37-44.

[115] PERESWETOFF-MORATH, L. (1998). Microspheres as nasal drug delivery systems. Advanced Drug Delivery Reviews, 29(1), 185-194.

[116] SOANE, R. J., HINCHCLIFFE, M., DAVIS, S. S., & ILLUM, L. (2001). Clearance characteristics of chitosan based formulations in the sheep nasal cavity. International Journal of Pharmaceutics, 217(1), 183-191.

[117] ILLUM, L. (2003). Nasal drug delivery: possibilities, problems and solutions. Journal of Controlled Release, 87(1), 187-198.

[118] KRAULAND, A. H., GUGGI, D., & BERNKOP-SCHNÜRCH, A. (2006). Thiolated chitosan microparticles: a vehicle for nasal peptide drug delivery. International Journal of Pharmaceutics, 307(2), 270-277.

[119] SCALIA, S., YOUNG, P. M., & TRAINI, D. (2015). Solid lipid microparticles as an approach to drug delivery. Expert Opinion on Drug Delivery, 12(4), 583-599.

[120] OTTO, D. P., OTTO, A., & DE VILLIERS, M. M. (2015). Differences in physicochemical properties to consider in the design, evaluation and choice between microparticles and nanoparticles for drug delivery. Expert Opinion in Drug Delivery. 12(5):763-777

[121] BHATT, R., SINGH, D., PRAKASH, A., MISHRA, N. (2015) Development, characterization and nasal delivery of rosmarinic acid-loaded solid lipid nanoparticles for the effective management of Huntington's disease. Drug Delivery. 22(7), 931-939.