ABSTRACT

The blood brain barrier (BBB) one of the strictest barriers of in-vivo therapeutic drug delivery. The barriers are restricted exchange of hydrophilic compounds, small proteins and charged molecules between plasma and central nervous system (CNS). For decades, BBB has prevented the use of many therapeutic agents for treating Alzheimer’s disease, stroke, brain tumor, head injury, spinal cord injury, depression, anxiety and other CNS disorders. The emerging approach is by passing the BBB by intranasal delivery, which provides a practical, noninvasive, rapid and simple method to deliver the therapeutic agents to the CNS. Intranasal delivery does not require any modification of the therapeutic agents. A wide variety of therapeutic agents, including both small molecules and macromolecules can be successfully delivered, including to the CNS, using the intranasal method. Advantage of intranasal delivery are Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic side effects and Avoids destruction in the gastrointestinal tract, hepatic “first pass” elimination and gut wall metabolism, allowing increased, reliable bioavailability.

KEYWORDS: Alzheimer’s disease; BBB; CNS; first pass elimination; intranasal delivery.

1. INTRODUCTION

The site-specific targeted drug delivery negotiates an exclusive delivery to specific pre-identified compartment with maximum intrinsic activity of drugs and concomitantly reduced access of the drug to irrelevant non-target cells. A number of strategies are followed to target...
various body tissue/organs. The brain is a delicate organ with many vital functions and formidable mechanisms isolate and defend it from the outside world. Unfortunately, the same mechanisms that prevent intrusive environmental chemicals accessing the brain also prevent the access of therapeutic chemicals. Hence, a number of strategies like invasive approach (blood–brain barrier (BBB) disruption, intracerebral implants), physiological approach (pseudonutrients, ligand binding proteins, chimeric peptides), pharmacological approach (liposomes, nanoparticles, nano-conjugates, chemical drug delivery) are used for targeting drug molecules to brain.\(^{[1,2]}\) The olfactory region of nasal mucosa that provides a direct connection between nose and brain can be exploited for targeting of CNS acting drug molecules used in conditions like Alzheimer’s disease, depression, migraine, schizophrenia, etc. Intranasal drug delivery system has been recognized as a reliable route for the administration of drugs next to parenteral and oral routes. Nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic drugs and also appears to be a favorable way to overcome the obstacles for the direct entry of drugs to the target site.\(^{[3]}\) This system has been accepted in the Ayurvedic system of Indian medicine and in the recent times, this is mostly preferred over the oral administration due to their better systemic bioavailability, as the gastrointestinal metabolism of the drug is avoided.\(^{[4]}\) This route is also painless, non invasive and tolerated favorably. There are several problems associated with targeting drugs to brain, especially the hydrophilic ones and those of high molecular weight. This is because of the impervious nature of the endothelium which divides the systemic circulation and barrier between the blood and brain.\(^{[5]}\) The olfactory region of the nasal mucosa provides a direct connection between the nose and brain, and by the use of nanoemulsions loaded with drugs, conditions such as Alzheimer’s disease, migraine, depression, schizophrenia, Parkinson’s diseases, meningitis, etc. can be treated.\(^{[6,7]}\) It is particularly more useful compared to oral and parenteral routes among pediatric patients as the former routes may increase the anxiety among them.\(^{[8]}\) Mistry et al. have reviewed the use of nanoparticles for the direct delivery of drugs from nose to brain. They also emphasize for the need for evaluating the toxicity of the nanoparticle delivery system through the nasal route.\(^{[7]}\) Preparation of nanoemulsions containing risperidone for its delivery to the brain via nose has been reported.\(^{[6]}\) It is inferred that this emulsion is more effective through the nasal rather than intravenous route. These types of emulsions can also be used as a non toxic mucosal adjuvant for influenza vaccine virus.\(^{[9]}\) Another application of intranasal drug delivery system in therapeutics is their use in development of vaccines. Immunity is achieved by the administration of mucosal antigen. Currently, the first intranasal vaccine has been
marketed. The nasal cavity is one of the most efficient sites because of its reduced enzymatic activity, high availability of immune active sites and its moderately permeable epithelium. Among the possible delivery systems, the use of nano based carriers hold a great promise to protect the biomolecules, promote nanocarrier interaction with mucosa and to direct antigen to the lymphoid tissues. Therefore the use of nanoemulsions in intranasal drug delivery system is set to bring about significant results in targeting drugs to the brain in the treatment of diseases related to central nervous system.

2. NANOEMULSION

Lipid-based formulations present a huge range of optional delivery systems such as solutions, suspensions, self-emulsifying systems and nanoemulsions. Among these approaches, oral nanoemulsions offer a very good alternative because they can improve the bioavailability by increasing the solubility of hydrophobic drugs and are now widely used for the administration of BCS class II and class IV drugs.

2.1 DEFINITION AND MEANING OF TERM NANOEMULSION

The word ‘nano’ is a Greek term which means dwarf. It refers to materials which are smaller in sizes usually in nanometer range or in other words one billionth of a meter. When materials are reduced to such extremely small particle sizes, they exhibit amazing phenomenon which in turn is utilized in nanotechnology and nanomedicine for a number of applications. Word ‘Microemulsion’ has also been used for nanoemulsion at places because of their similarity in structure, method of formation and applications in drug delivery. Microemulsions are the result of nearly seventy years of research, starting when Hoarand Schulman in 1943 first introduced the concept of micro emulsion after they mixed a milky solution with hexanol to obtain a clear, single-phase and non-conducting solution. They defined the term “microemulsion” as an optically isotropic and transparent oil and water (O/W) dispersion consisting of approximately equal volumes of the two phases. In 1981, microemulsions were defined as systems of water; oil and amphiphilc that were single optically isotropic and thermodynamically stable liquid solutions. No indication of size was stated but the size of particles was typically between 5 and 100 nm. The word microemulsion is often a misnomer and should not be used for droplets with diameters of less than 100 nm. This limit size is often cited in nanotechnology regulatory publications. Therefore to reduce any confusion in the terminology, word micro emulsion should only be used if droplet size exceeds 100nm. Nanoemulsions are defined as thermodynamically stable transparent
isotropic dispersions of oil and water stabilized by an interfacial film of surfactant and co
surfactant molecules having the droplet size of less than 100nm. The observed transparency
of these systems is due the fact that the maximum size of nanoemulsion droplets is less than
the one-fourth of the wavelength of visible light (approximately 150 nm).\textsuperscript{[19]} Both micro
emulsions and nanoemulsions can be translucent solutions with as light sky-blue
opalescence.\textsuperscript{[20]} Droplet size in thermodynamically stable nanoemulsions is usually 10-100
nm.\textsuperscript{[21,17,18,22]}

![Figure 1: Visual difference between nanoemulsion (A) and macroemulsion (B)](image)

2.2 STRUCTURE, SHAPE AND STABILITY OF NANOEMULSION

Structure of a nanoemulsion depends upon the components present in the system. They may
form one, two, three or more separate phases that are in equilibrium with each other.
Structurally, these phases are classified as water-continuous (oil in water type), oil-
continuous (water in oil type), or bi continuous systems depending on the concentrations,
nature and arrangements of the molecules present within. The structures in these phases may
be spheroid (e.g., micelles or reverse micelles), cylinder-like (such as rod-micelles or reverse
micelles), plane-like (e.g., lamellar structures), or sponge-like (e.g., bi continuous).\textsuperscript{[23]} In w/o
nanoemulsion, water droplets are dispersed in the continuous oil phase while o/w
nanoemulsion is formed when oil droplets are dispersed in the continuous aqueous phase. In
systems where the amounts of water and oil are similar, a bi continuous nanoemulsion may
result. In all three types’ of nanoemulsion system, the interface is stabilized by an appropriate
combination of surfactants and/or co-surfactants. The mixture of oil, water and surfactants is
able to form a wide variety of structures and phases depending upon the proportions of the
components. The flexibility of the surfactant film is an important factor in this regard. A
flexible surfactant film will enable the existence of several different structures like droplet like shapes, aggregates and bi continuous structures, and therefore broaden the range of nanoemulsion region. A very rigid surfactant film will not enable existence of a stable nanoemulsion structure. It is the concentration of components and method of formation which differentiates a nanoemulsion from a macro emulsion. Similarities and differences among nanoemulsion, microemulsion and an emulsion in presented in the figure 2.

<table>
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<th></th>
<th>macroemulsions</th>
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<th>microemulsions</th>
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<td>thermodynamically unstable, kinetically stable</td>
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<td>high &amp; low energy methods</td>
<td>low energy method</td>
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<tr>
<td><strong>polydispersity</strong></td>
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<td>typically low (&lt;10-20%)</td>
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</table>

Figure 2: Comparison of macroemulsions, nanoemulsions (also referred to as miniemulsions) and microemulsions with respect to size, shape, stability, method of preparation, and polydispersity. Nanoemulsions and microemulsions have a larger surface area per unit volume than do microemulsion because of their size. In addition, due to a strong kinetic stability, nanoemulsions are less sensitive to physical and chemical changes. The nanoemulsion TEM image has been reprinted with permission.

As indicated in definition, a nanoemulsion is thermodynamically and kinetically stable system. However, if proper attention is not given while manufacturing such systems the general problem that may be encountered is Ostwald ripening or molecular diffusion, flocculation, sedimentation, coalescence and creaming of the formed nanoemulsion. It may
become unstable if some of the components undergo chemical changes during storage, or if the environmental conditions are altered into a range where the system is no longer thermodynamically stable. For example, a nanoemulsion may breakdown if it is diluted or if its temperature is changed, which commonly happens during the manufacturing, storage and utilization of nanoemulsion-based products. The small droplet size of nanoemulsion confers stability against sedimentation (or creaming) because the Brownian motion and consequently the diffusion rate are higher than the sedimentation (or creaming) rate induced by the gravity force.\textsuperscript{[25]} The interfacial tension in nanoemulsion is made sufficiently low so that interfacial energy become comparable or even lower than the entropy of the dispersion. In this case, the free energy of the system becomes zero or negative. This explains the thermodynamic stability of nanoemulsion. Thus, the main driving force for nanoemulsion formation is the ultra-low interfacial tension, which is usually achieved by the use of two or more emulsifiers, one predominantly water soluble and other predominantly oil soluble called co-surfactant and reduces the interfacial tension ($\gamma$) to the order of $<10^{-2}$ m/Nm generally required for the nanoemulsion formation.\textsuperscript{[26]} Overall, the stability of nanoemulsion is achieved by presence of Brownian motion and ultra-low interfacial tension within the nanoemulsion system.

2.3 ADVANTAGES OF NANOEMULSION\textsuperscript{[22, 27]}

- It can be used as substitute for liposome’s and vesicles.
- Improves the bioavailability of drug.
- Non-toxic and non-irritant in nature.
- Improved physical stability.
- Nanoemulsions have small-sized droplets having larger surface area providing better absorption.
- It can be formulated in variety of formulations such as foams, creams, liquids, and sprays.
- Provides better uptake of oil-soluble supplements in cell culture technology.
- Helpful to solubilize lipophilic drug.
- Helpful in taste masking.
- Lesser amount of energy is required.

3. BLOOD BRAIN BARRIER (BBB)

The BBB consists of walls of capillaries that separate brain from circulating blood. In the human brain there are approximately 100 billion capillaries that have a net surface area of near 20 square meters. Despite its enormous surface area, the BBB lacks intercellular cleft
and fenestrae and significantly restricts the entry of solutes to the brain from the periphery. Its low permeability is attributed, in large part, to BMVEC (Bovine Brain Microvascular Endothelial Cells) which forms tight junctions and has low pinocytic activity\[28,29,30\] some relatively lipophilic and small molecular weight substances can transport across the BMVEC by passive diffusion. However, a large number of lipophilic compounds are rapidly effluxed from the brain into the blood by extremely effective drug efflux systems expressed in the BBB.\[31, 32\] These efflux systems include P-glycoprotein (Pgp), multidrug resistance proteins (MRPs), breast cancer resistance protein (BCRP) and the multi-specific organic anion transporter (MOAT). There is also an enzymatic barrier to drug transport in the BMVEC. Activity of several enzymes that participate in the metabolism and inactivation of endogenous compounds, such as g-glutamyl transpeptidase, alkaline phosphatase, and aromatic acid decarboxylase is elevated in cerebral micro vessels.\[33,34\]

4. NASAL ABSORPTION
4.1 EPITHELIAL CELL BARRIER
The olfactory and the respiratory epithelium in the nasal cavity both are tightly connected via intercellular junctions that surround the cells of the epithelium. There are three major junctional complexes, the zona occludens nearby the apical surface (normally referred to as the tight junction), below the zona adherence and below that the macula adherence. The tight junction comprises a chain of integral membrane proteins that interact with the components of the cytoskeleton through other proteins. The key components in the extracellular cell to cell contacts between adjacent epithelial cells are the transmembrane proteins occludin and claudin and the junctional adhesion molecule, JAM. The NH2 and COOH termini of the occludin are situated in the cytoplasm of the cell and the COOH interacts (are anchored to) the N–termini of the scaffolding proteins ZO-1, ZO-2 and ZO-3 present in the cytoplasm, which again is connected to the F-actin.\[35\] The extracellular loops of the occludin will interact with loops from occludin from a neighbouring cell to promote the sealing of the intercellular space; the tight junction. Multiple regulatory pathways control the structure and function of the tight junction, usually involving phosphorylation and de-phosphorylation processes.\[36\] Phosphorylation of the tight junctional proteins apparently regulates the formation of the junction itself and likely also the function of the junction. A disruption of the interaction of the junctional proteins would have a direct effect on the paracellular transport of drugs. It is known that Protein Kinase C (PKC) inhibitors increase paracellular permeability and that this is the mechanism of action of chitosan, whereby it transiently can
open tight junctions. The diameter of the tight junction of the nasal epithelial cells have been measured to be between 3.9 – 8.4 Å and even with the use of absorption enhancers the maximal diameter reached when opened was in the region of 15 nm.\textsuperscript{[37]}  for this reason, the need for absorption enhancers to permit the paracellular transport of peptides and proteins is obvious with for example the diameters of an insulin monomer being 26.8 Å, cytochrome C 35 Å, peroxidase 40 Å and lysozyme 35 - 45 Å.\textsuperscript{[38,39,40]}  It is also obvious that even an open tight junction will not allow the paracellular passage of nanoparticles of diameters (50–500nm) generally used in nasal drug delivery.

4.2 NASAL TRANSPORT ROUTES

Nasally administered drugs will be deposited on the respiratory (pseudostratified columnar) epithelium. The site of deposition of formulations administered by means of a normal nasal spray device is generally in the anterior part of the nose, but several specialised devices are able to deposit the formulation wider and higher in the cavity, reaching the superior turbinates and the olfactory region.\textsuperscript{[41]}  From the site of deposition, dependent on the character of the drug i.e. molecular weight, charge and lipophilicity, the drug can be absorbed through the epithelium and reach the systemic circulation or can be cleared via the nasopharynx down the gastrointestinal tract by the mucociliary clearance system. The mucociliary clearance mechanism comprises cilia, originating on the surface of the columnar epithelial cells, which are mobile and beat in a synchronized fashion, thereby enabling the propelling of the viscous upper part of the mucus layer covering the cells, posteriorly towards the nasopharynx, with a rate of about 5 mm/min. There is also the possibility of enzymatic degradation of the drug in the nasal cavity by various enzymes such as cytochrome-P450 dependent monooxygenase, aldehyde dehydrogenase, peptidases and proteases. It has been shown that the cytochrome-P450 enzyme activity in the olfactory region of the nasal epithelium is higher than in the liver.\textsuperscript{[42]}  Due to the direct access to the systemic circulation from the nasal cavity, drugs absorbed bypass the first pass metabolism of the liver.

The drug can reach the CNS by three main pathways
i)  Direct paracellular or transcellular transport via the olfactory neurons or olfactory epithelial cells (‘olfactory neural pathway’).
ii)  Transport via the trigeminal nerves (‘trigeminal pathway’).
iii) Drugs that have been absorbed into the systemic circulation can, if sufficient lipophilic, cross the blood brain barrier into the CNS (‘systemic pathway’).\textsuperscript{[43,44]}
The olfactory neurones terminate at the apical surface of the olfactory epithelium as small bulbous knobs and are hence in contact with the environment in the nasal cavity. From here the neurons pass through the lamina propria where they, in bundles with other neurones, pass through the cribriform place and synapse in the olfactory bulb. In contrast, the two branches of the trigeminal nerve that have nerve endings in the nasal cavity, the maxillary nerve and the mandibular nerve, are not directly exposed to the lumen of the nasal cavity, but lie in the epithelium near the apical surface terminating at the level of the tight junctions.\textsuperscript{[45]} Hence, in order to reach and enter the nerves the drug will have to cross the epithelium by means of paracellular or transcellular routes. The trigeminal nerves have trans-synaptic connections mainly with the hindbrain, but also, part of the trigeminal nerve passes through the cribriform plate and hence will attach to the forebrain.\textsuperscript{[46]}

5. ADVANTAGES OF INTRANASAL ROUTE\textsuperscript{[47]}

\begin{itemize}
  \item Provide painless accessibility and needle free drug application.
  \item Administration of drug with no necessity of trained personnel facilitates (self-medication).
  \item Improving patient compliance compared to parenteral routes.
  \item Provide good penetration especially lipophilic, low molecular weight drugs throughout the nasal mucosa.
  \item It provides quick absorption and rapid onset of action due to a relatively large absorptive surface and high vascularization.
  \item Nasal administration of suitable drugs would therefore be effective in emergency therapy as substitute to parenteral administration routes.
  \item It avoids the hepatic first-pass metabolism and thus potential for dose reduction compared to oral delivery.
  \item Potential for direct delivery of drugs to the central nervous system through the olfactory region under bypassing the blood-brain-barrier.
  \item Direct delivery of vaccine to lymphatic tissue and secretory immune response at distant mucosal sites.
\end{itemize}

6. DISADVANTAGES OF INTRANASAL ROUTE

\begin{itemize}
  \item Limited to potent drugs/small volumes (25–200μl).
  \item Active mucociliary clearance.
\end{itemize}
7. LIMITATIONS OF INTRANASAL ROUTE

- Enzymatic degradation by nasal cytochrome P450/peptidases/proteases (pseudo first-pass effect).
- Low permeability for hydrophilic drugs without absorption enhancers necessitates large doses.
- Low pH of nasal epithelium.
- Low CNS delivery efficiencies for proteins measured thus far (≤0.05%).

8. REASON FOR DEVELOPMENT OF NASAL DELIVERY

Nasal drug delivery is a useful delivery system for drugs that are active in small doses and show minimal or no oral bioavailability. The nasal path circumvents hepatic first pass elimination associated with the oral delivery; it is simply accessible and suitable for self-medication. Presently, two classes of nasally delivered therapeutic agents in the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. The second class encompasses a small amount of drugs, which have sufficient nasal absorption for display systemic effects. Main candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in the gastrointestinal tract, poor absorption properties, and their speedy and extensive biotransformation.

9. FACTORS AFFECTING NASAL DRUG ABSORPTION

Different factors affect bioavailability of nasally administered drugs as follows;

- Biological Factors
  - Structural features
  - Biochemical changes

- Physiological factors
  - Blood supply and neuronal regulation.
  - Nasal secretions.
• Mucociliary clearance and ciliary beat frequency.
• Pathological conditions.
• Environmental conditions.
• Membrane permeability.

➤ Physicochemical Properties of Drugs.
• Molecular weight.
• Size.
• Solubility.
• Lipophilicity.
• pka and Partition coefficient.
• Polymorphism.
• Chemical state.
• Physical state.

➤ Physicochemical Properties of Formulation.
• Physical form of formulation.
• pH.
• Osmolarity.
• Volume of solution applied and drug concentration.
• Viscosity.

9.1 Biological factors

9.1.1 Structural features
There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharynx. These structures and the category of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds.\[49\]

9.1.2 Biochemical changes
Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a huge number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants,
alcohols, nicotine and cocaine due to p450 dependent monoxygenase system. Protease and peptidase were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations different approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin.\textsuperscript{[50]}

9.2 Physiological factors

9.2.1 Blood supply and neuronal regulation
Nasal mucosa is extremely permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the increase and decrease in the amounts of drug permeated, respectively.\textsuperscript{[51]} Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

9.2.2 Nasal Secretions
Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is about 1.5–2 l ml daily. The permeability of drug through the nasal mucosa is affected by:

- **Viscosity of nasal secretion**
  The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of drug is affected due to impairment of mucociliary clearance by changing the time of contact of drug and mucosa.

- **Solubility of drug in nasal secretions**
  For permeation of drug solubilisation is compulsory and the drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.

- **Diurnal variation**
  Nasal secretions also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.
- **pH of nasal cavity**
  Variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrate molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the character of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.\(^{[52]}\)

**9.2.3 Mucociliary clearance (MCC) and ciliary beating**
When a substance is nasally administered, it is cleared from the nasal cavity in~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.

**9.2.4 Pathological conditions**
Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases like common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

**9.2.5 Environmental conditions**
Moderate reduction in the rate of MCC occurs at the temperature of 24°C, it has been predicted that a linear increase in ciliary beat frequency occurs with raise in temperature.

**9.2.6 Membrane permeability**
Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The high molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability thus absorbed through endocytic transport in smaller amounts.\(^{[53]}\)

**9.3 Physicochemical properties of drug**
**9.3.1 Molecular weight and size**
Drug permeation determined by the molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly
predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don’t significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

9.3.2 Solubility
Most important factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have low solubility in the aqueous secretions. Water soluble drugs are absorbed through passive diffusion and lipophilic drugs through active transport depending on their solubility.\(^{[54]}\)

9.3.3 Lipophilicity
The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of several drugs is decreased due to excess hydrophilicity in such cases prodrug approach is useful.

9.3.4 pKa and partition coefficient
As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile main factor governing nasal absorption is partition coefficient.\(^{[55]}\)

9.3.5 Polymorphism
Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form development for the nasal delivery.\(^{[56]}\)
9.3.6 Chemical state of drug
Absorption of the drug is determined by the chemical form of the drug in which is presented to nasal mucosa. Chemically modify drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated.\[56\]

9.3.7 Physical state of drug
Particle size and morphology of drug are two most important properties for particulate nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils.\[56\]

9.4 Physicochemical properties of formulation
9.4.1 Physical form of formulation
Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.

9.4.2 pH
Extent of drug ionization determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and avoid growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children.

9.4.3 Osmolarity
Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred. Some scientist studied the effects of formulation osmolarity, on the nasal absorption of secretin in rats. They found that all cells of the nasal mucosa were affected by
the concentration of sodium chloride in the formulation and the absorption reached a maximum at 0.462 M sodium chloride concentration. At this concentration shrinkage of epithelial cells was observed. Hence tonicity is also having impact on drug absorption.[57]

9.4.4 Volume of solution applied and drug concentration

There is no constant link between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9% and 26.7% of days the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined.[58]

9.4.5 Viscosity

Contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thus increasing the time for permeation.

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Drug delivery system</th>
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10. CONCLUSION

A successful drug delivery system is one which offers commercial applicability to pharmaceutical industry for large-scale production. CNS drug delivery is multifaceted due to restrictions imposed through the BBB. Direct nose-to-brain (intranasal) drug delivery system is a potential approach to overcome the obstacles presented by the BBB. Intranasal drug delivery bypasses the BBB to target CNS and reducing the systemic exposure of drug, thus
reducing the systemic side effects. Intranasal route of administration an attractive option of drug delivery due to its non-invasiveness. NE based drug delivery systems can open up exciting possibilities in the treatment of brain disorders. Intranasal administration is a practical and non-invasive strategy and holds promise for brain targeting. NE based nasal sprays could provide an excellent drug delivery alternative for the treatment of brain related clinical conditions which require quick onset of action. NE could provide additional therapeutic benefits. Moreover, multifunctional NE can be considered as “next generation” colloidal lipidic carriers for brain targeting.

REFERENCES


