Review Article

A RECENT REVIEW ON NASAL MICROEMULSION FOR TREATMENT OF CNS DISORDER

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ABSTRACT

Nasal route is found to be valuable for targeting drugs to CNS via a different mechanism. The advantages, disadvantages, various aspects of nasal anatomy and physiology, mechanism of drug transport from nose brain, drug selection criteria to cross BBB/Blood-CSF barrier are discussed briefly. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects. There are various approaches in delivering a therapeutic substance to the target site. One such approach is using microemulsion as a carrier for the drug. The main purpose of this study is the use of microemulsion technology in drug targeting to the brain along with mechanism of the nose to brain transport, formulation and formation of the microemulsion and its characterization.

Keywords: Nasal drug delivery, Microemulsion, Nose to brain transport, Drug carrier, Target site

INTRODUCTION

As estimated by WHO, depression shall become the second largest illness in terms of morbidity by another decade in the world. Depression is a common, generally chronic, and debilitating psychiatric condition. It is increasingly recognised that depression affects the entire body including painful physical symptoms that may be part of a broader cluster of symptoms that constitute a major depressive disorder, not merely emotional symptoms (mood and anxiety). Because depression impacts all body systems it is no surprise that investigations attempting to determine the effects of depression on hormones, neurotransmission, brain imaging, sleep architecture, immune function, and so on, have tended to identify differences between depressed patients and normal subjects. The researchers found that intranasal administration was associated with strong improvement in depression.

Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of medication in the remaining tissues. Thus improving the efficacy of the drug and reducing side effects. Intranasal drug delivery–practiced for thousands of years, and given a new impact of life. Many scientists have reported evidence of nose-to-brain transport. Many previously abandoned potent CNS drug candidates promise to become successful CNS therapeutic drugs vial intranasal delivery.

The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurvedic system of Indian medicines [1]. The early 1980s saw the introduction of the nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. The early 1980s saw the introduction of the nasal route as a promising systemic delivery alternative to other conventional drug delivery routes. Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. The Oral administration of protein and peptide drug is not possible because they are significantly degraded in the gastrointestinal tract or considerably metabolized by the first-pass effect in the liver. Intranasal drug delivery offers a promising alternative route for administration of such drugs. Many advanced and effective approaches to the CNS delivery of drugs have emerged in recent years. Intranasal drug delivery is one of the focused delivery options for

brain targeting as brain and nose compartments are connected to each other via olfactory/trigeminal route via peripheral circulation. Direct nose to brain transport results into rapid and/of higher uptake in the brain, which provides an alternative option of self-medication. Synthesis of more lipophilic analogues, enzyme inhibitors, permeation enhancers, colloidal, bioadhesive and novel drug delivery systems like microemulsion, liposomes and nanoparticles could help in eliminating certain pharmaceutical challenges like low bioavailability, local irritation and toxicity upon long term usage. With all its inherent advantages intranasal route has been indicated as the most promising approach for delivery of drugs to the brain/CNS.

Advantages of nasal drug delivery system [3, 4]

1. Rapid absorption and onset of action of drugs.

2. Elicitation of local immune response in respiratory infections such as influenza.

3. Ability to overcome first pass metabolism associated with oral medication of drugs.

4. Self-medication is possible.

5. The nasal bioavailability for smaller drug molecules is good.

6. Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.

7. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.

8. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

9. Drugs possessing poor stability in GIT. Fluids are given by nasal route.

10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

11. Easy accessibility and needle-free drug application without the necessity of trained personnel facilitates self-medication, thus improving patient compliances compared to parenteral routes.

12. Good penetration of, especially lipophilic, low molecular weight drugs through the nasal mucosa. For instance, the absolute nasal bioavailability of fentanyl is about 80%.

13. Rapid absorption and fast onset of action due to relatively large

absorption surface and high vascularization. Thus, the tmax of fentanyl after nasal administration was less than or equal to 7 minutes comparable to intravenous [i. v]. Nasal administration of suitable drug would, therefore, be effective in emergency therapy as an alternative to parenteral administration routes.

Disadvantages of nasal drug delivery system

1. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

2. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.

3. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.

4. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation

5. The nasal cavity provides smaller absorption surface area when compared to GIT.

6. Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.

7. Nasal congestion due to cold or allergies may interfere with this method of delivery.

8. Frequent use of this route may result in mucosal damage

9. Concentration achievable in different regions of the brain and spinal cord varies with each agent

10. Delivery is expected to decrease with increasing molecular weight of the drug.

11. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.

Nasal anatomy and physiology

In humans and other animal species, the major functions of the nasal cavity are breathing and olfaction. Researchers became interested in the nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa [5]. The nose is the primary entrance to the respiratory tract, allowing air to enter into the body for respiration. In humans and other animal species, the major functions of the nasal cavity are breathing and olfaction. Post drug administration into the nasal cavity, a solute can be deposited at one or more of anatomically distinct regions, the vestibular, respiratory and olfactory regions. The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 150 cm^2 23 and is divided into two nasal cavities via the septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm^2. Post drug administration into the nasal cavity, a solute can be deposited at one or more of here anatomically distinct regions, the vestibular, respiratory and olfactory region [5] that are distinguished according to the anatomical and histological structure in fig. 1, 2 and table 1 along with details given below.
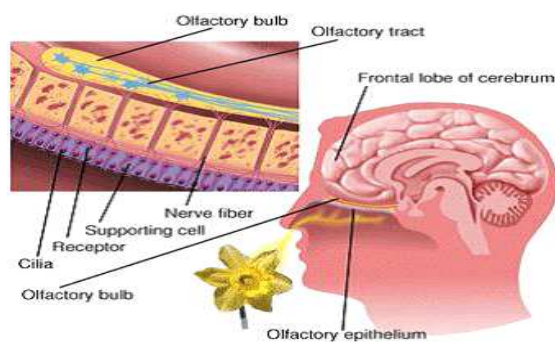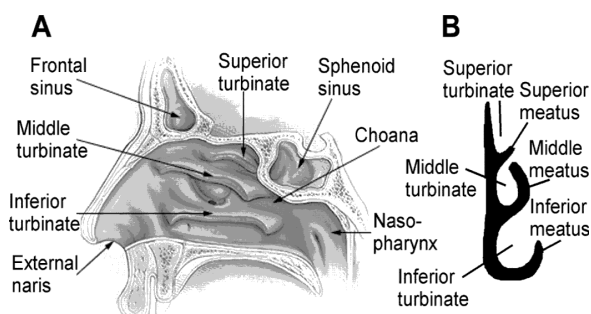

Fig. 1: Nasal mucosa

Fig. 2: Anatomy and histology of human nasal cavity

The respiratory region

The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it is divided in superior, middle and inferior turbinate's which are projected from the lateral wall. These specialised structures are responsible for humidification and temperature regulation of inhaled air. Between them, there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity [6]. The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells, These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia (where applicable). They may also serve to prevent drying of the mucosa by trapping moisture.

The olfactory region

It is of about 10 cm2 in surface area and plays a vital role in the transportation of drugs to the brain and the CSF. The olfactory region comprises of thick connective tissue, lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, bowans bundle and blood vessels whereas the epithelium consists of three different cell types, basal cells, supporting cells, and olfactory receptor cells. Neurones are interspersed between supporting cells. The olfactory receptor cells are bipolar neurones with a single dendritic, extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extends above the epithelium. The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10 to 15 min [7]. The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 15 to 20 min. numerous enzymes, for instance, cytochrome P450 enzymes, carboxylesterases and glutathione S-transferases are found in nasal cavity [8].

The vestibular region

This is located at the opening of nasal passages and is responsible for filtering out airborne particles. It is considered to be the least important of the three regions with regard to drug absorption.

Biopharmaceutical consideration

The easy accessibility and higher surface area make 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 [6]. Comprehending the factors that can affect drug deposition, retention and absorption are essential to enable the 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. 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 fig. 3

Table 1: human nasal epithelium characteristics

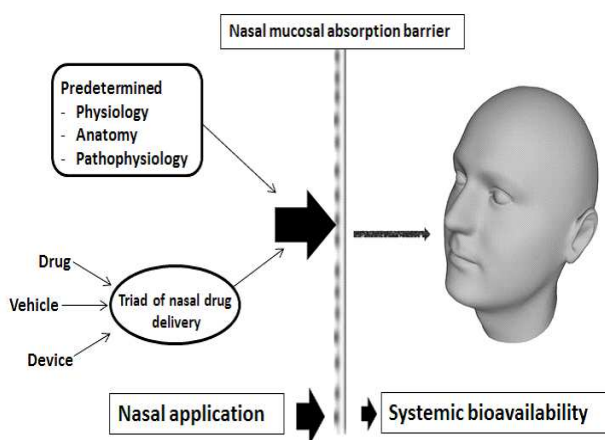| Nasal section	Epithelial characteristics cells/functions	Surface area	Vascularization	Permeability
Vestibule	Stratified squamous and keratinized epithelial cells with nasal hairs/Support and protection	≈ 0.6 cm2	low	Poor
Atrium	Stratified squamous cells/Support-Pseudo stratified cells/Support	≈ 0.6 cm2	low	Reduced
Respiratory Region	Columnar non-ciliated cells/Support Columnar ciliated cells/Support and muciliary clearance Globet cells/Mucus secretion Basal cells/Progenitors of other cell types	≈ 130 cm2	Very high	Good
Olfactory Region	Sustentacular cells/Support and synthetic Olfactory receptor cells/Olfaction Perception Basal cells/Progenitors of other cell types	≈ 15 cm2	high	Direct access to CNS

Fig. 3: Consideration of formulation elements of nasal product development

Mechanism of nose to brain drug transport

It is important to examine the pathway/mechanisms involved prior to addressing the possibilities to improve transnasal uptake by the brain [9, 10]. The olfactory region is known to be the portal for a drug substance to enter from nose-to-brain following nasal absorption. Thus, transport across the olfactory epithelium is the predominant concern for brain-targeted intranasal delivery shown in fig. 2.
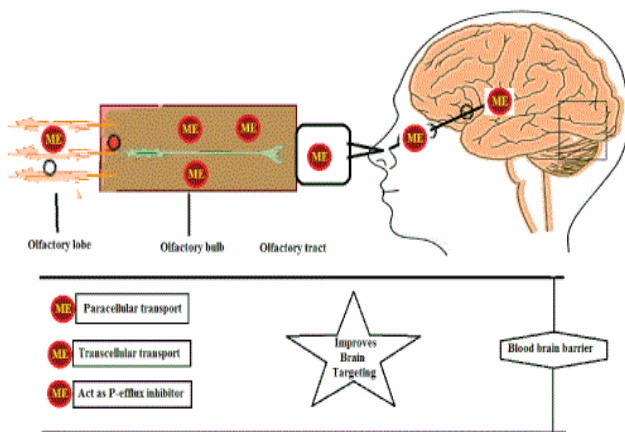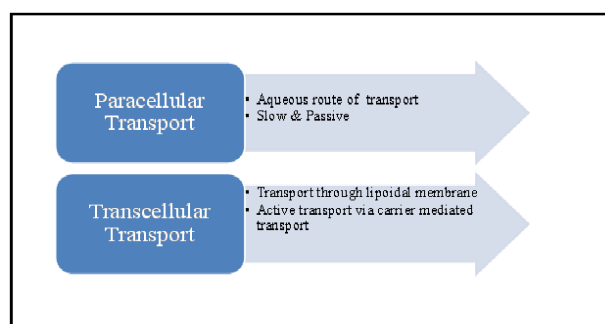

Fig. 4: Nose to brain targeting

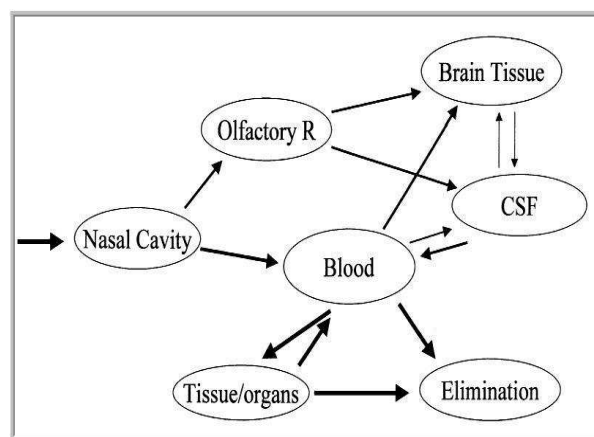**Fig. 5: Mechanism of nose to brain drug transport**

Fig. 6: Mechanism of nose to brain drug transport

Nasal mucosa and subarachnoid space; lymphatic plexus located in nasal mucosa and subarachnoid space along with perineural sheaths in olfactory nerve filaments and subarachnoid space appear to have communications between them. The nasal drug delivery to the CNS is thought to involve either an intraneuronal or extraneuronal pathway [11, 12]. A drug can cross the olfactory path by one or more mechanism/pathways. These include paracellular transport by movement of the drug through interstitial space of cells transcellular or simple diffusion across the membrane or receptor/fluid phase mediated endocytosis and transcytosis by vesicle carrier and neuronal transport. The paracellular transport mechanism/route is slow and passive. It mainly uses an aqueous mode of transport. Usually, the drug passes through the tight junctions and the open clefts of the epithelial cells present in the nasal mucosa. There is an inverse log-log correlation between intranasal absorption and the

molecular weight of water soluble compounds. Compounds, which are highly hydrophilic in nature and/or of low molecular weight, are most appropriate for paracellular transport. A sharp reduction in absorption and poor bioavailability was observed for the drugs having a molecular weight greater than 1000 Da. Moreover, drugs can also cross cell membranes by a carrier–mediated active transport route. For example, chitosan, a natural biopolymer from shellfish, stretches and opens up the tight junctions between

epithelial cells to facilitate drug transport. The transcellular transport mechanisms/ pathways mainly encompass transport via a lipoidal route [13, 14]. The drug can be transported across the nasal mucosa/epithelium by either receptor mediated endocytosis or passive diffusion or fluid phase endocytosis transcellular route. Highly lipophilic drugs are expected to have rapid/complete transnasal uptake. The olfactory neurone cells facilitate the drug transport principally to the olfactory bulb.

Table 2: Nose-to-brain transport of drug molecules and possible pathways

Pathways	Molecules
Nasal mucosa → sensory nerve cells of olfactory epithelium → subarachoid space → blood stream	Albumin
Nasal mucosa→ olfactory nerve fiber	Amino acids
Nasopharyngeal epithelium→ lymphatic→ cervical lymphatic vessel→ blood vessel	Rabbit virulent type III Pneumococci
Nasal mucosa→ cerebrospinal fluid and serum	Dopamine, Estradiol
Nasal membrane→ olfactory dendrites→ nervous system→ supporting cells in the olfactory mucosa→ submucosal blood vascular system	Norethindrone Progesterone
Nasal membrane → peripheral circulation and CSF → CNS	Norethisterone
Nasal mucosa→ peripheral and cranial nerves→ CNS	Herpes virus encephalitis

Drug selection properties to penetrate blood-brain/blood-CSF barriers [15]

1. The Smaller molecular size of drug (>300 Da).

2. Moderately lipophilic drugs are good candidates for the nose to brain targeting.

3. The volume of distribution near about 1 lit/kg.

4. The drug must be a not strong ligand of an efflux pump at BBB/Blood-CSF barrier.

Factors influencing nasal absorption of drugs [6]

A. Physicochemical properties of drugs

a. Chemical form

The chemical form of a drug is important in determining absorption. For example, conversion of the drug into a salt or ester form can also alter its absorption. Huang *et al.*, 1985 studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

b. Polymorphism

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

c. Molecular weight

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da [8] Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. The apparent cut-off point for molecular weight is approximately 1,000 with molecules less than 1,000 having better absorption. The shape is also important. Linear molecules have a lower absorption than cyclic–shaped molecules.

d. Particle size

It has been reported that particle sizes greater than 10μm are deposited in the nasal cavity. Particles that are 2 to 10 μm can be retained in the lungs and particles of less than 1 μm are exhaled.

e. Solubility and dissolution rate

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs

B) Formulation factors

A. pH of the formulation

Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimise systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5.22 Also, volume and concentration are important to consider. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 μL/nostril have been suggested.

- To avoid irritation of nasal mucosa;
- To allow the drug to be available in unionised form for absorption;
- To prevent growth of pathogenic bacteria in the nasal passage;
- To maintain functionality of excipients such as preservatives; and
- To sustain the normal physiological ciliary movement.

Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5 keeping in mind the physicochemical properties of the drug as drugs are absorbed in the unionised form.

B. Buffer capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200μL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

C. Osmolarity

Drug absorption can be affected by tonicity of the formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution. Suzuki *et al.*, 1999 showed that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

D. Solubilizers

The aqueous solubility of the drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol

monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrin such as HP-β-cyclodextrin that serve as a biocompatible Solubilizers and stabiliser in combination with lipophilic absorption enhancers.

E. Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Van De Donk *et al.*, 1980 have shown that mercury-containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in the nasal systems.

F. Antioxidants

Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxyl toluene and tocopherol.

G. Humectants

Many allergic and chronic diseases are often connected with crusts and drying of the mucous membrane. Adequate intranasal moisture is essential for preventing dehydration.

Therefore humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

H. Drug concentration, dose and dose volume

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

I. Role of absorption enhancers

Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by aminopeptidases. Osmolarity and pH may accelerate the enhancing effect. Examples of enhancing agents are surfactants, glycosides, cyclodextrins and glycols. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme inhibition.

C) Physiological factors

a. Effect of deposition on absorption

Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability while posterior portion of the nose where the drug permeability is generally higher provides shorter residence time.

b. Nasal blood flow

Nasal mucosal membrane is very rich in the vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

c. Effect of mucociliary clearance

The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered. A prolonged residence time in the nasal cavity may also be achieved by using bioadhesive polymers or by increasing the viscosity of the formulation.

d. Effect of enzymatic activity

Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and aminopeptidase at the mucosal membrane. The level of aminopeptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin (Igs) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.

e. Effect of pathological condition

Intranasal pathologies such as allergic rhinitis, infections, or previous nasal surgery may affect the nasal mucociliary transport process and/or capacity for nasal absorption. During the common cold, the efficiency of an intranasal medication is often compromised. Nasal clearance is reduced in insulin dependent diabetes. Nasal pathology can also alter mucosal pH and thus affect absorption.

Microemulsions as a drug delivery system for brain targeting

Emulsions are a heterogeneous system in which one immiscible liquid is dispersed as droplets in another liquid. Such a thermodynamically unstable system is kinetically stabilized by addition of one further component or a mixture of components that exhibit emulsifying properties. One emulsion that is further dispersed into another continuous phase is called double emulsion, multiple emulsion or emulsified emulsion. The droplet-size distribution of emulsion droplets is 0.5-50.0µm. The inner droplet size distribution of w/o emulsion in multiple emulsions is usually smaller than 0.5µm, whereas the outer, external multiple emulsions is quite large and can exceed 10µm. Another emulsion system is "microemulsion" and can define a system of water, oil and amphiphile, which is a single optically isotropic. The droplets in a microemulsion are in the range of 0.1-1.0µm. The existence of this theoretical structure was later confirmed by use of various technologies and we can today adopt the definition given by Attwood as follows: "A microemulsion is a system of water, oil and amphiphilic compounds (surfactant and co-surfactant), which is a transparent, single optically isotropic and thermodynamically stable liquid". The difference between the appearance of emulsion and microemulsion given in fig. 6 and table 3.

Fig. 6: Difference between appearance of emulsion and microemulsion

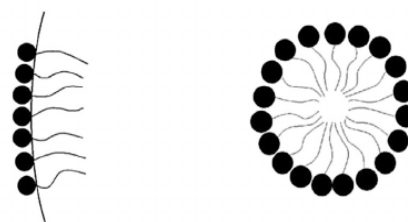| Emulsion	Microemulsion
Unstable, will eventually separate	Thermodynamically stable
Relatively large droplets (1-10 mm)	Small aggregates (~10 nm)
Relatively static system	Highly dynamic system
Moderately large internal surface, moderate amount of surfactant	High internal surface, high amount of surfactant needed
Small oil/water curvature	The oil/water interfacial film can be highly curved

Table 3: Showing difference between emulsion and microemulsion [16-21]

Types of microemulsion [22]

Three types of microemulsions are most likely to be formed depending on the composition

1) O/W microemulsion

In the case of oil-in-water (O/W) microemulsions, droplets are formed with the surfactant's head-groups oriented towards the continuous water phase and the nonpolar tails grouped inside the hydrophobic core of the aggregate. Fig. 2(a) is an idealized schematic representation of this type of microemulsion.

2) W/O microemulsion

In oil-rich microemulsions, water is solubilised as small droplets surrounded by a membrane of surfactant and cosurfactant molecules, as shown schematically in fig. 2(c). These structures are known as water-in-oil (W/O) microemulsions, where the lipophilic parts of the surfactants are directed towards the oil phase and their polar head groups are directed towards the water phase. At high water concentration, microemulsions consist of small oil droplets dispersed in water, whereas at lower water concentrations the situation is reversed and the system consists of water droplets dispersed in oil. In each phase, the oil and water are separated by the surfactant-rich film. In general w/o systems can be prepared at higher disperse phase concentrations than o/w systems, especially when ionic surfactants are used. The oil droplets in o/w microemulsions are surrounded by the electric double layers, which can extend into the external phase for a considerable distance (up to 100 nm), depending on the electrolyte concentration.
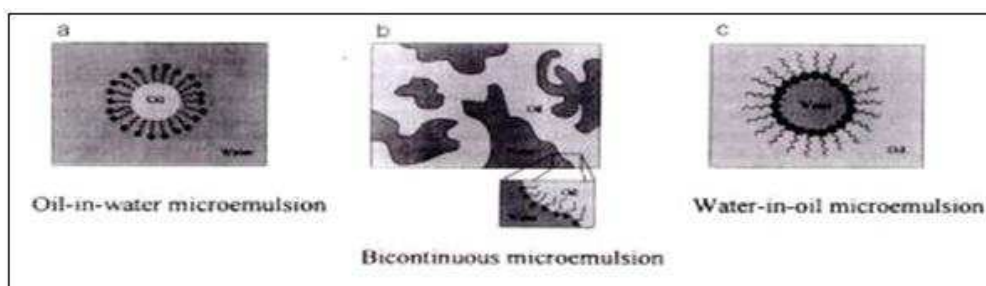

Fig. 7: Three most commonly encountered microemulsion microstructures, (a) oil-in-water, (b) bicontinuous, and (c) water-in-oil microemulsion

Bicontinuous phases

In many cases, it is possible to effect a gradual transition from O/W to W/O microemulsion simply by changing the volume fraction of oil and water. The intermediate region, which contains approximately equal volumes of oil and water, is often composed of bicontinuous structures where both the oil and the water domains extend over macroscopic distances and the surfactant forms an interface of rapidly fluctuating curvature, but in which the net curvature is near zero. [fig. 7(b)]

Challenges in nose to brain drug delivery via microemulsion

The main problem in a microemulsion application is a high concentration and a narrow range of physiologically acceptable surfactants and co-surfactants [23, 24]. Large surfactant concentration (10-40%) determines their stability [25]. Selection of components: if the systems are to be used topically, selection of components involves a consideration of their toxicity, irritation and sensitivity [26]. Nasal congestion due to cold or allergies may interfere with absorption of the drug through the nasal mucosa. Delivery is expected to decrease with increasing molecular weight of the drug. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa. Concentration achievable in different regions of the brain and spinal cord varies with each agent. The fluidity of interfacial film should be low to promote the formulation of microemulsion [27]. Components of Microemulsion Formulations: A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsions. The emphasis is, therefore, on the use of Generally Regarded As Safe (GRAS) excipients.

Oil phase

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail group region to a greater extent than long chain alkanes, and hence swell this region to a greater extent, resulting in increased negative curvature (and reduced effective HLB) [28]. Saturated (for example, lauric, myristic and capric acid) and unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) have penetration enhancing a property of their own and they have been studied since a long time. Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase. Lipophilic drugs are preferably solubilized in o/w microemulsions. The main criterion for selecting the oil phase is that the drug should have high solubility in it. This will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form.

Surfactants

The surfactant chosen must be able to lower the interfacial tension to a very small value which facilitates dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. It is generally accepted that low HLB surfactants are favoured for the formulation of w/o microemulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation.

Cosurfactants

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form [29-31]. The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition [32-34]. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short or contain fluidising groups (e. g. unsaturated bonds). Short to medium chain length alcohols (C3-C8) are commonly added as cosurfactants which further reduce the interfacial tension and increase the fluidity of the interface.

Method of preparation

Phase titration method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help

of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time-consuming and difficult to interpret, the pseudo-ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component (fig. 4). The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included. The methodology has been comprehensively discussed by Shafiq-un-Nabi *et al.* [35] (fig. 7).
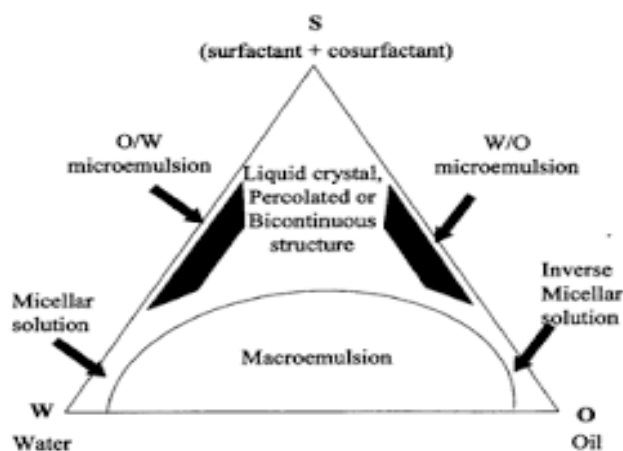

Fig. 8: Pseudo-ternary phase diagram of oil, water and surfactant showing microemulsion region

Phase inversion method

Phase inversion of microemulsions occurs upon addition of an excess of the dispersed phase or in response to temperature. During phase inversion, drastic physical changes occur including changes in particle size that can affect drug release both *in vivo* and *in-vitro*. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as a phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially, water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilising a w/o microemulsion to an o/w microemulsion at the inversion locus. Short-chain surfactants form flexible monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point.

Application of microemulsion in brain targeting

Treatment of epilepsy and schizophrenia

Vyas *et al.*, prepared mucoadhesive microemulsion for the antiepileptic drug clonazepam [36]. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to

8 h following intranasal administration of clonazepam mucoadhesive microemulsion compared to i. v. was found to be 2-fold higher, indicating the larger extent of distribution of the drug in the brain. Kwatikar *et al.*, prepared microemulsion containing valproic acid showed a fractional diffusion efficiency and better brain bioavailability efficiency [37]. Hence microemulsions are the promising approach for delivery of valproic acid to the brain for treatment of epilepsy. Florence *et al.*, prepared clobazam microemulsion and mucoadhesive microemulsion. Formulations were assessed for the average onset of seizures in pentylenetetrazole treated mice. This study demonstrated high brain targeting efficiency of prepared clobazam mucoadhesive microemulsion and delayed onset of seizures induced by pentylenetetrazole in mice after intranasal administration of developed formulation [38]. Further clinical evaluation of the developed formulation may result in a product suitable for the treatment of acute seizures due to status epileptics and patients suffering from drug tolerance and hepatic impairment on chronic use in the treatment of epileptics, schizophrenia and anxiety. Shende *et al.*, prepared microemulsion of lomotrigone from nose to brain delivery. Intranasal administration allows transport of the drug to the brain circumventing the BBB, thus providing the better option to target drug to the brain with a quick onset of action in case of emergency in epilepsy [39]. Lorazepam (LZM) is a poorly water-soluble drug which can be used as a tranquillizer, muscle relaxant, sleep inducer, sedative and antiepileptic agent [40]. Co-solvent based parenteral formulations, however, have several disadvantages, such as pain and tissue damage at the site of injection and precipitation of the drug on dilution in several cases [41]. Furthermore, parenteral administration of the organic co-solvents can also cause hemolysis [42]. Amit *et al.*, Prepared lorazepam microemulsions and demonstrated that microemulsion has very low hemolytic potential and exhibit good physical and chemical stability and can be considered as a viable alternative to the currently marketed lorazepam formulations [43].

Treatment of a migraine

Migraine treatment has evolved in the scientific arena, and opinions differ on whether a migraine is primarily a vascular or a neurological dysfunction [44]. Sumatriptan is rapidly but incompletely absorbed following oral administration and undergoes the first-pass metabolism, resulting in a low absolute bioavailability of 14% in humans [45]. The transport of Sumatriptan across the blood-brain barrier (BBB) is very poor [46]. Studies have demonstrated that intranasal administration offers a practical, noninvasive, alternative route of administration for drug delivery to the brain [47, 48].

Vyas *et al.*, prepared mucoadhesive microemulsion of Sumatriptan which shows rapid and larger extent of selective Sumatriptan nose-to-brain transport compared with suspension and microparticles of the same in rats. Enhanced rate and extent of transport of Sumatriptan following intranasal administration of microemulsion may help in decreasing the dose and frequency of dosing and possibly maximise the therapeutic index [49]. Shelke *et al.*, reported that zolmitriptan microemulsion via nose to brain delivery provides the dual advantages of enhanced bioavailability, with rapid onset of action in the treatment of a migraine [50]. Tushar *et al.*, investigated zolmitriptan microemulsions (ZTME) for rapid drug delivery to the brain to treat acute attacks of a migraine and to characterise microemulsions and evaluate biodistribution in rats. Studies of this investigation conclusively demonstrated rapid and larger extent of transport into the rat brain following intranasal administration of ZTME and can play a promising role in the treatment of acute attacks of a migraine [51].

As an antidepressant

Tiwari *et al.*, developed eucalyptus oil microemulsion for intranasal delivery to the brain [52]. This work demonstrated that the microemulsion of eucalyptus oil is cost effective and an efficient formulation which provides the rapid onset in soothing stimulant and antidepressant action.

Treatment of angina pectoris and neurological deficit

Qizhi Zhang 90 prepared this microemulsion to improve the solubility and enhance the brain uptake of nimodipine (NM), which

was suitable for intranasal delivery. The uptake of NM in the olfactory bulb from the nasal route was three folds compared with intravenous (i. v.) injection. The ratios of AUC in brain tissues and cerebrospinal fluid to that in plasma obtained after nasal administration were significantly higher than those after i. v. administration. These results suggest that a microemulsion system is a promising approach for intranasal delivery of NM for the treatment and prevention of neurodegenerative diseases. Jing Yao 91 prepared hyaluronic acid chitosan-based microemulsion (HAC-ME) containing nobiletin to determine its distribution in mice brain following i. v. administration. Based on AUC0–t, MRT and Cmax, HAC-ME delivered more nobiletin to the brain compared to nobiletin solution. These results indicate that HAC-ME may be potential candidates for drugs delivered into the brain.

Treatment of amnesia

Jogani and Misra, 2008 studied microemulsion and mucoadhesive microemulsion of tacrine, assessed its pharmacokinetic-pharmacodynamics performances for brain targeting and for improvement of memory in scopolamine-induced amnesic mice [53, 54]. The results demonstrated rapid and larger extent of transport of tacrine into the mice brain and faster regain of memory loss in scopolamine-induced amnesic mice after intranasal microemulsion administration.

Intranasal delivery of non-peptides and peptides

Oral administration of peptides is impossible because of gastrointestinal enzymatic degradation and hepatic first-pass effects. Increasing evidence suggests that the intranasal route of administration may be an attractive and convenient option for the delivery of certain compounds to the brain. In fact, several peptides and non-peptides including luteinizing-hormone-releasing hormone, oxytocin, calcitonin, and vasopressin, are routinely administered intranasally in clinical practice, and other peptides, including insulin, glucagon, growth hormone, growth hormone-releasing hormone, and somatostatin, are currently under investigation.

CONFLICT OF INTERESTS

Declare none

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