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A RECENT REVIEW ON INTRANASAL MICROEMULSION: A NOVEL DRUG CARRIER SYSTEM

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ABSTRACT

Nasal drug delivery has been used as an another route for the systemic availability of drugs restricted to intravenous administration. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in fast systemic drug absorption. 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. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a cosurfactant with a droplet size usually in the range of 10-100 nm. 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[1,2]

Nasal therapy is the recognized form of treatment in the Ayurvedic systems of Indian medicine, and also called as nasaya karma. Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is

permeable to more compounds than the GIT tract due to lack of gastric enzymatic activity, neutral and pancreatic pH of the nasal mucus and low dilution by GIT contents. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. Less drug absorption of proteins and peptides via the nasal delivery is due to the mucociliary clearance mechanism. The nasal route circumvents hepatic first pass elimination associated with the oral delivery. It is easily accessible and suitable for self-medication.

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. The word microemulsion was originally proposed by Schulman et al. (1959)1. They prepared a quaternary solution of water, benzene, hexanol, and k-oleate which was stable, homogenous and slightly opalescent. These systems became clear as soon as a short chain alcohol was added. In the years between 1943 and 1965 Schulman and co-workers described how to prepare these transparent systems.

Microemulsions system are thermally stable isotropic systems in which two immiscible liquids, one is water and second is oil are mixed to form a single phase by means of an appropriate surfactant. The short to medium chain alcohols are generally considered as cosurfactants in the microemulsion system. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low. Therefore microemulsions form spontaneously, with an average droplet diameter of 10 to 140 nm. It was only in 1959 that Schulman proposed to call these systems microemulsions.

Advantages of nasal drug delivery system[3,4]

1) Drug degradation that is observed in the gastrointestinal tract is absent.
2) Hepatic first pass metabolism is avoided.
3) Rapid drug absorption and quick onset of action can be achieved.
4) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
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) 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 g.i.t. fluids are given by nasal route.
10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery system.

Disadvantages[3,4]

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT. 4) 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) Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.
5) 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.

Nasal Anatomy And Physiology[5,9]

The nasal cavity has a total volume of about 16 to 19 ml and a total surface area of about 150 cm^2 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 24 that are distinguished according to anatomical and histological structure.

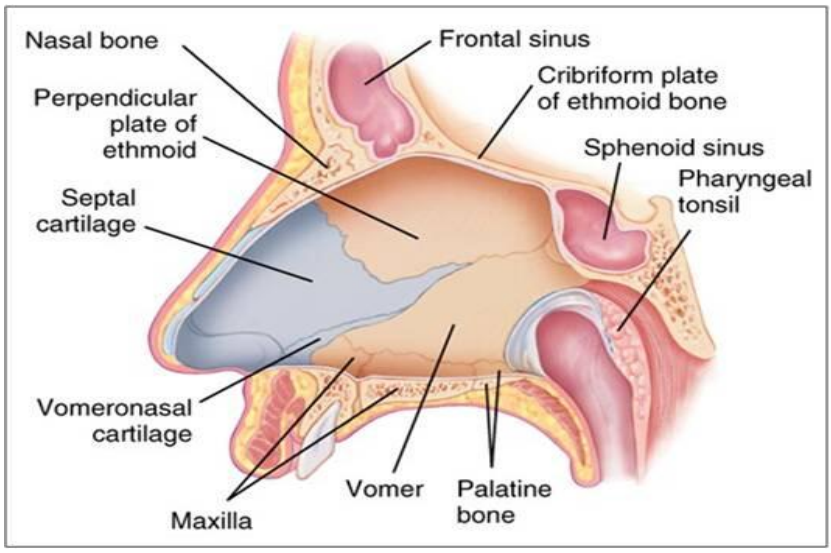

Fig. 1: Anatomy and histology of human nasal cavity.

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. 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 cm^2 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 tissue 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. The mucosal secretions pH 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.

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.

Mechanism of Nasal Absorption[3,4]

The absorbed drugs from the nasal route should pass through the mucus layer. It is the first step in absorption. Unchanged small drugs easily pass through mucus layer but large and charged drugs are difficult to cross it. The principle protein of the mucus is mucin which has the tendency to bind to the solutes, hindering diffusion.

The two mechanisms that include there

a. First mechanism

First mechanism is an aqueous transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water soluble compounds. The molecular weight greater than 1000 Daltons show poor bioavailability.

b. Second mechanism

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

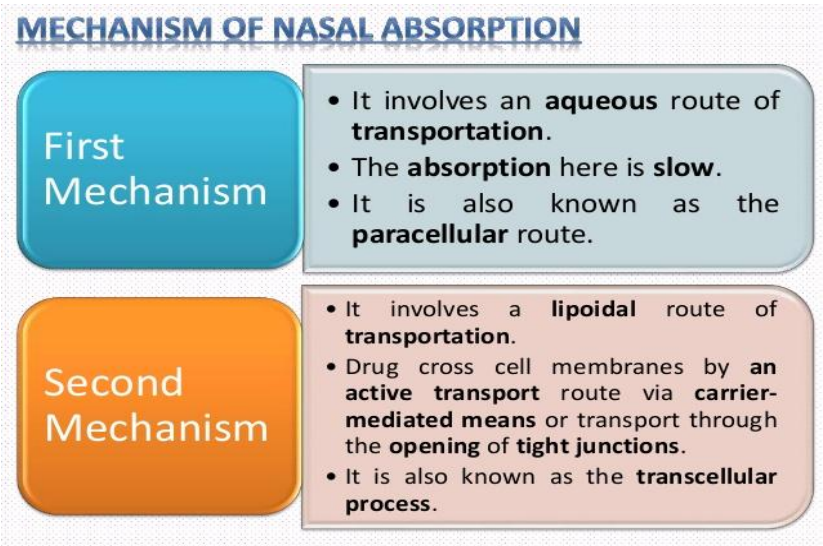

Fig. 2: Mechanism of nose to brain drug transport.

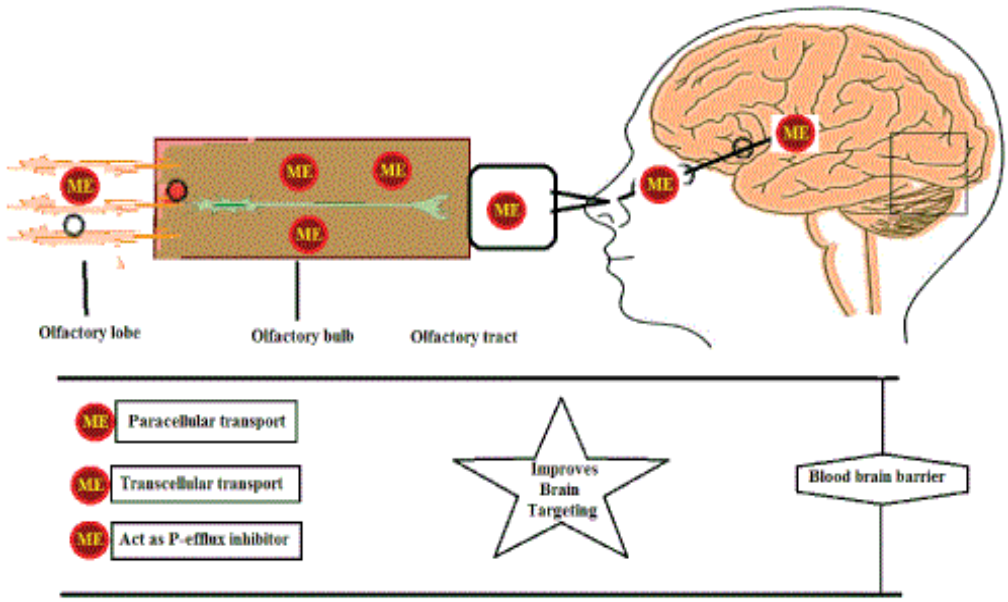

Fig. 3: Mechanism of nose to brain drug transport.

Drug selection properties to penetrate blood- brain/blood-csf barriers

1. Smaller molecular size of drug (>300 da).
2. Moderately lipophilic drugs are good candidates for nose to brain targeting.
3. Volume of distribution near about 1 lit/kg.
4. Drug must be not strong ligand of an efflux pump at BBB/Blood CSF barrier.
5. Drugs including fluroquinolones and other anti-infective such as isoniazide, pyrizinamides, linezolode, fluconazoles, metronidazole reach csf to serum ratio = 1 (AUC).

Factors Influencing Nasal Absorption of Drugs

Some of the physiological factors and physicochemical, formulation are imperative and must be considered prior to designing intranasal delivery for brain targeting.

1) Physicochemical properties of drugs

a. **Chemical form:**[12] Chemical form of a drug is necessary in determining absorption. example, when there is conversion of the drug into a salt or ester form can change its absorption. Huang et al., 1985 studied the effect of structural modification of drug on absorption. And it was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly more than that of L-Tyrosine.

b. **Polymorphism:** This affect the solubility and dissolution rate of drugs and their absorption via biological membranes.

c. **Molecular Weight:** Linear inverse correlation has been reported between the molecular weight and absorption of drugs up to 300 Da. 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. Shape is also important. Linear molecules have lower absorption than cyclic – shaped molecules.

d. **Particle Size:** It has been reported that particle sizes more 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 & dissolution Rate:** Both the dissolution and solubility are necessary factors in nasal absorption from powders and suspensions. Particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles, no absorption occurs.

2) FORMULATION FACTORS

a. pH of the formulation

The pKa of a particular drug and pH of the nasal cavity need to be considered to optimize systemic absorption. Nasal irritation is redused when products are delivered with a pH range of 4.5 to 6.5. Also, volume and concentration are important to consider. The 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 unionized form for absorption;

- To prevent growth of pathogenic bacteria in the nasal passage;
- To maintain functionality of excipients such as preservatives; and
- To sustain normal physiological ciliary movement.

b. Buffer Capacity

c. 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.

d. Osmolarity

e. The drug absorption is affect by the tonicity of formulation. Shrinkage of epithelial tissue has been observed in the presence of hypertonic solutions. Hypertonicsaline 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.

c. Solubilizers:[13]

f. Aqueous solubility of drug is 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 chainglycerides and Labrasol can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP-βcyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers.

d. Preservatives:[11]

g. Most of the 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.

e. Antioxidants: Usually, antioxidants do notcause nasal irritation or affect drug absorption. 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.

f. **Humectants:** Many allergic and chronic diseases are often connected with crusts and drying of 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.

g. **Drug Concentration, Dose & Dose Volume:** Volume of administration and drug concentration, dose are three parameters that impact the performance of the nasal delivery performance. Nasal absorption of LTyrosine was shown to increase with drug concentration in nasal perfusion experiments.

h. **Role of Absorption Enhancers:** The absorption enhancers may be required when a drug exhibits low membrane permeability, more molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. pH and osmolarity and 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 nasal blood flow, increasing membrane fluidity, and decreasing mucus viscosity.

Physiological factors

a. Effect of Deposition on Absorption

Deposition of the drug 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 rich in vasculature and plays a important 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 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 contact 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

Few 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 amino-peptidase 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

The intranasal pathologies such as allergic, rhinitis, or pervious 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 less in insulin dependent diabetes. Nasal pathology can also alter affect absorption mucosal and thus pH.

Microemulsions as a drug delivery system for brain targeting

Microemulsions are the isotropic, thermally stable translucent systems of oil, surfactant and water, frequently in combination with a cosurfactant with a droplet size usually in the range of 10-100 nm.

“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”. 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 0.11.0μm.

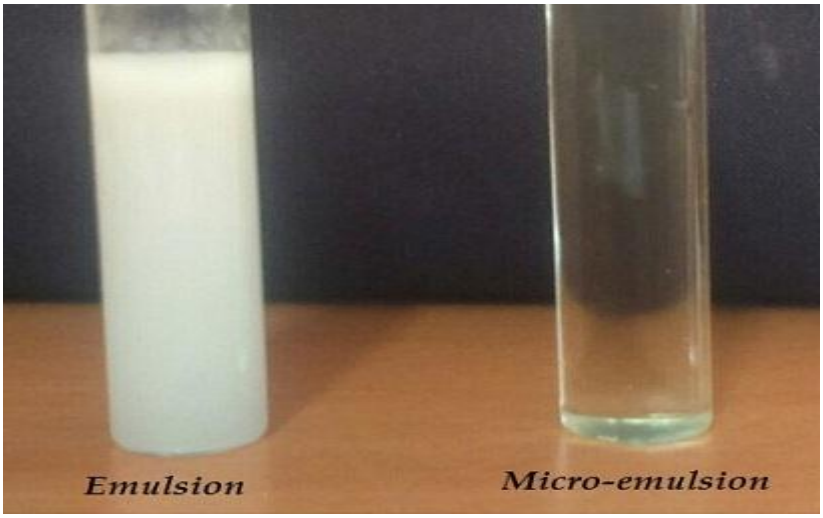

Fig. 4: Emulsion Vs Microemulsion.

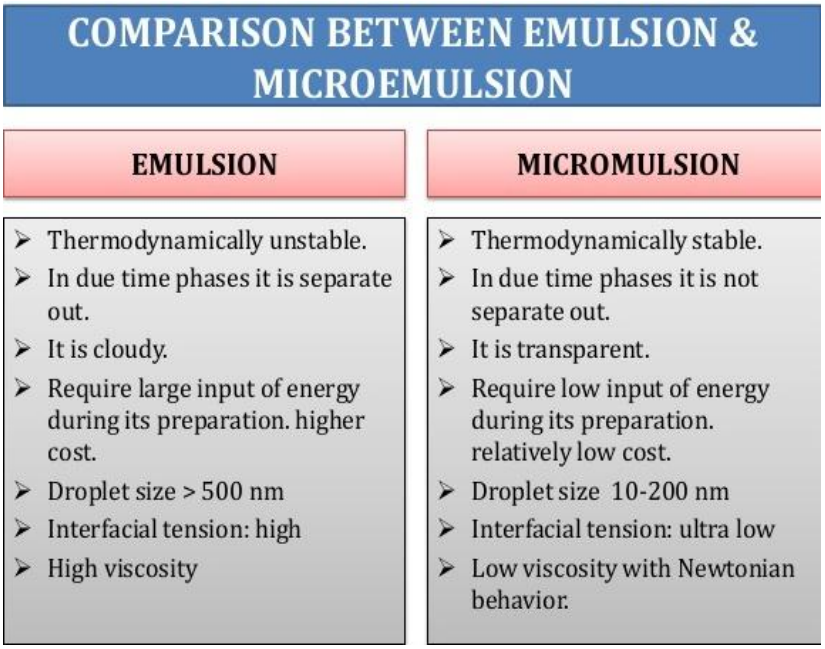

Fig. 5: Difference between Emulsion and Microemulsion.

Types of microemulsion[14]

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

1. Oil in water (O/W) microemulsions wherein oil droplets are dispersed in the continuos aqueous phase.

2. Water in oil (W/O) microemulsions wherein water droplets are dispersed in the continuous oil phase;

3. Bi-continuous microemulsions wherein microdomains of oil and water are interdispersed within the system. In all the three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

Advantages of Microemulsion[15,16]

1. Provides a aqueous dosage form for water insoluble drugs.
2. Various routes like tropical, oral and intravenous can be used to deliver the drugs.
3. Helps in solubilization of lipophillic drug hence Increase the rate of absorption and bioavailability of drugs.
4. Eliminates variability in absorption.
5. Wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
6. Ease of manufacturing and scale-up.
7. Helpful in taste masking.
8. Rapid and efficient penetration of the drug moiety.
9. Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.
10. Liquid dosage form increases patient compliance.
11. Long shelf life as compared to other colloidal drug delivery system.
12. Improve therapeutic efficacy of drugs and allow reduction in the volume of the drug delivery vehicle, thus minimizing toxic side effects.
13. Easy to administer in child and adults who have difficulty swallowing solid dosage forms.

Why microemulsions are chosen for nasal to brain drug delivery

Literature survey revealed that intranasal administration of microemulsion offers a practical, noninvasive, alternative route of administration for drug delivery to the brain. Intranasal administration allows transport of drugs to the brain circumventing BBB, thus providing better option to target drugs to the brain. Microemulsion lower the skin irritation: alcohol-free microemulsions have been reported with much lower irritation potential.

Challenges In Nose To Brain Drug Delivery Via Microemulsion[17,21]

The main issue in a microemulsion application is a more concentration and a narrow range of physiologically acceptable surfactants and co-surfactants. Large surfactant concentration (10-40%) determines their stability. Selection of components: if the systems are to be used topically, selection of components involves a consideration of their toxicity, irritation and sensitivity.

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.

Components of Microemulsion: A more number of surfactants and oils are available which can be used as components of microemulsion systems but their, irritation potential, unclear mechanism and toxicity 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.

Components of Microemulsion Formulations[22,26]

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 nonaggressive microemulsions.

Oil phase

Oil component shows curvature by its ability to penetration 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). Unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) and Saturated (for example, lauric, myristic and capric acid) have penetration enhancing a property of their own and they have been studied since a long time. Fatty acid esters such as ethyl and oleic acid have also been employed as the oil phase. Lipophilic drugs mainly solubilized in o/w microemulsions. The main criteria 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.

Examples of Oils

Ethyl oleate, Mineral oil, Isopropyl myristate, Decanol, Oleic acid, Vegetable oils (Coconut oil, Safflower oil, Soyabean oil, Olive oil), Medium chain length triglyceride (Mygliol 812).

Surfactants

Surfactant in the formulation must be lower the interfacial tension to a very less 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 mostly 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.

Example of Surfactants

Polysorbate (Tween 80 and Tween 20), Lauromacrogol 300, Lecithins, Decyl polyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oleique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG- 8 caprylic/capril glyceride (Labrasol).

Cosurfactants

In most of the cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form. 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. 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.

Example Of Co-surfactants

Sorbitan monooleate, Sorbitan monostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy)ethanol (Transcutol P) and Ethanol.

METHOD OF PREPARATION OF MICROEMULSION

Phase titration method[27]

Microemulsions are prepared by using 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. The microemulsions are formed 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 pseudoternary 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. The region can be separated into o/w or w/o microemulsion by simply considering the composition that is whether it is water rich and oil rich. Observations should be made carefully so that the metastable systems are not included.

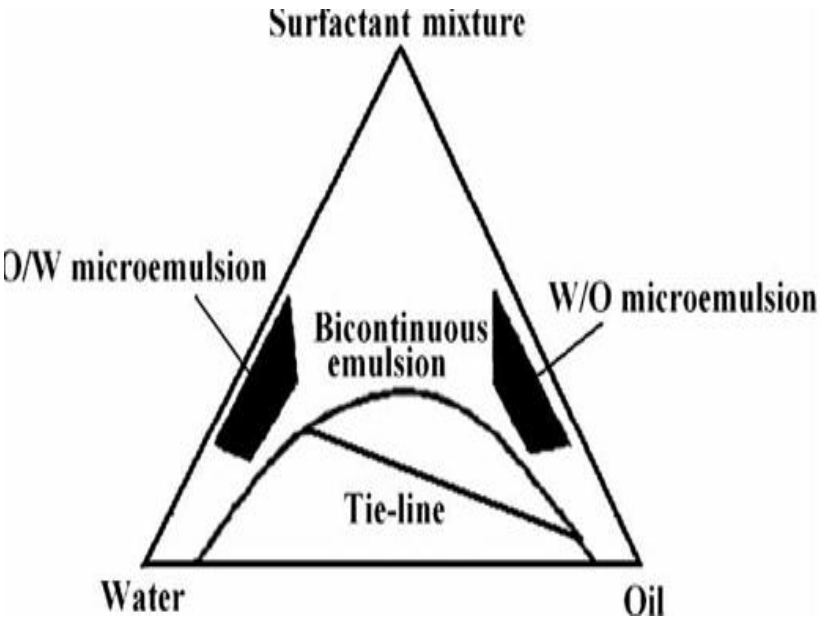

Fig. 6: Pseudo-ternary phase diagram of oil, water and surfactant showing microemulsion region.

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. Shortchain surfactants form flexible monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point.

Application Of Microemulsion In Brain Targeting

1. As an antidepressant:[28]

Tiwari et al., developed eucalyptus oil microemulsion for intranasal delivery to the brain. 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.

2. Treatment of Epilepsy and schizophrenia

Vyas et al.[29], prepared mucoadhesive microemulsion for the antiepileptic drug clonazepam. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to 8 hours following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2-fold higher, indicating larger extent of distribution of the drug in the brain.

Kwatikar et al.[30], prepared microemulsion containing valproic acid showed a fractional diffusion efficiency and better brain bioavailability efficiency, Hence microemulsions are the promising approach for delivery of valproic acid to the brain for treatement of epilepsy.

Shende et al.[31], 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 quick onset of action in case of emergency in epilepsy.

Lorazepam (LZM) is a poorly water-soluble drug which can be used as tranquillizer, muscle relaxant, sleep inducer, sedative and antiepileptic agent.[32] 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.[33]

Furthermore, parenteral administration of the organic co-solvents can also cause hemolysis. Amit et al.[34], Prepared lorazepam microemulsions and demonstrated that microemulsion have 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.[35]

3. Treatment of migraine[36]

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

Vyas et al.[41], 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 maximize the therapeutic index.

Shelke et al.[42], reported that zolmitriptan microemulsion via nose to brain delivery provides the dual advantages of enhanced bioavailability, with rapid onset of action in treatment of migraine. Tushar et al., investigated zolmitriptan microemulsions (ZTME) for rapid drug delivery to the brain to treat acute attacks of migraine and to characterize 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 migraine.[88]

4. Treatment of amnesia[44]

Jogani and Misra, 2008 studied microemulsion and mucoadhesive microemulsion of tacrine, assessed its pharmacokinetic-pharmacodynamic performances for brain targeting and for improvement of memory in scopolamineinduced amnesic mice. 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.

5. Intranasal delivery of non peptides and peptides[45,46]

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-hormonereleasing 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.

6. Intranasal delivery of vaccine

The nasal delivery of vaccines is an attractive option. This route of delivery avoids the discomfort and hazards associated with injection and provides improved local immune protection and cross protection in distant mucosal sites. It is important however to improve distribution to the nasal mucosa, while at the same time limiting deposition outside the target sites. Achieving this balance is essential in improving the reproducibility, safety, clinical efficacy and patient compliance of nasally delivered vaccines and potent drugs.

7. Intranasal delivery of Analgesics[47]

Pain management and nasal drug delivery clearly combine to meet the needs of a growing and underserved marketplace. The convergence of pain management and nasal drug delivery may prove to be very fortuitous to those who are suffering with acute, moderate-to severe and breakthrough pain. Nasal delivery of analgesics will offer a non-invasive, fast-acting, efficacious means to relieve that pain. Intranasal delivery of morphine offers several advantages such as rapid onset, and fewer GI side effects.

CONCLUSION

Microemulsions have proved to be very useful formulations on commercial scale for nasal delivery of water insoluble drugs. With the appropriate selection of the excipients, it is also possible to design a nasal microemulsion with desired characteristics such as controlled release. Microemulsions have a much more solubilizing capacity for non-polar organic drugs compare to aqueous micellar solutions. The microemulsion system might be a promising approach for the rapid-onset intranasal delivery of drugs in the treatment of brain disorders such as epilepsy and migraine, and allergic conditions.

REFERENCES

1. Schulman JH, Stoekenius W, Prince LM, "Mechanism of Formation and Structure of Microemulsions by Electron Microscopy", The Journal of Physical Chemistry, 1959; 63: 1677–1680.
2. Chhabra V, Free ML, Kang PK, Truesdail SE, Shah DO, "Microemulsion as an emerging technology", Tensile Surfactant Detergents, 1997; 34: 156–168.
3. Gannu Praveen Kumar*1, S. Kiran2, Strategies And Prospects Of Nasal Drug Delivery System. International Journal of Pharmaceutical Science And Research, 2012; 3(3): 648-658.
4. Dr.Pravin Chaudhari, A Review On Recent Trends In Nasal Drug Delivery, 2006.
5. Mygind N, Dahl R. Anotomy, Physiology And Function of the nasal cavities in health and disease. Adv Drug Deliv Reviews, 1998; 29: 3-12
6. Candace L.G. and Pollock G.M., Nasal Drug administration: Potential for targeted central nervous system. Delivery. J. Pharm. Sci., 2005; 94: 187–95.
7. Huang CH, Kimura R, Nassar RB, Hussain A. Mechanism of nasal absorption of drugs I: Physicochemical parameters influencing the rate of in situ nasal absorptions of drugs in rats. J Pharm Sci., 1985; 74: 608-11.
8. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci, 2002; 5: 514-6.
9. Dowley AC, Homer JJ. The effect of inferior turbinate hypertrophy on nasal spray distribution to the middle meatus. Clin Otolaryngol, 2001; 26: 488-90.
10. Roland Nau, Fritz Sorgel and Helmut Eiffert, Penetration of Drugs through the Blood-Cerebrospinal Fluid/Blood-Brain Barrier for Treatment of Central Nervous System Infections Clin. Microbiol. Rev., October, 2010; 23(4): 858-83.
11. Van De Donk HJM, Muller Plantema IP, Zuidema J, Merkus FWHM. The effects of preservatives on the cilliary beat frequency of chicken embryo tracheas. Rhinology, 1980; 18: 119-130.
12. Huang C, Kimura R, Nassar A, Hussain A. Mechanism of nasal drug absorption of drug II: absorption of L-tyrosine and the effect of structural modification on it‟s absorption. J Pharm Sci., 1985; 74: 298-1301.
13. Gattefosse bulletin. New lipidic systems enhancing the bioavailability of problem drugs, 1997; 1-81.
14. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. Crit Rev Therapeut Drug Carrier Syst, 1999; 16: 461- 21.

15. Aboofazeli R, Lawrence MJ. Investigations into the formation and characterization of phospholipid microemulsions: I Pseudo-ternary phase diagrams of systemscontaining water–lecithin–alcohol–isopropyl myristate, Int. J. Pharm., 1993; 161–75.
16. Nastruzzi C Gambari R., Antitumar activity of transdermally delivered aromatic tetra-amidines. J Controll release; 1994; 29: 53.
17. Corswant C, Thoren P, Engstrom S. Triglyceride-based microemulsion for intravenous administration of sparingly soluble substances. J Pharm Sci., 1998; 87: 200.
18. Aboofazeli R, Patel N, Thomas M, Lawrence MJ. Investigations into the formation and characterization of phospholipid microemulsions. IV. Pseudo-ternary phase diagrams of systems containing water-lecithin-alcohol and oil; the influence of oil. Int J Pharm., 1995; 125: 107-16.
19. Shinoda R, Kunieda H. Condition to produce so-called microemulsion: factors to increase the mutual solubility of oil and water by solubilizer. J Colloid Interface Sci., 1973; 42: 381.
20. Siebenbrodt I, Keipert S. Poloxamer-system as a potential ophthalmic microemulsion. Eur J Pharm Biopharm, 1993; 39: 25-30.
21. Attwood D. In: Colloidal drug delivery system. ed. Kreuter J. Marcel Dekker, New York, 1994; 31.
22. Hargava HN, Narurkar A, Lieb LM. Using Microemulsions for drug delivery. Pharm Tech, 1987; 11: 46-52.
23. Kreuter J. Microemulsions. In: Colloidal drug delivery systems. New York: Marcel Dekker, 1994; 31-71.
24. Lawrence MJ. Surfactant systems: microemulsions and vesicles as vehicles for drug delivery. Eur J Drug Metab Pharmacokinet, 1994; 3: 257-69.
25. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Delivery Rev., 2000; 47: 89-121.
26. Aboofazeli R, Lawrence CB, Wicks SR, Lawrence MJ. Investigations into the formation and characterization of phospholipid microemulsions III. Pseudo-ternary phase diagrams of systems containing water-lecithin-isopropyl myristate and either an alkanoic acid, amine, alkane diol, poly ethylene glycol alkyl ether or alcohol as co-surfactant. Int J Pharm., 1994; 111: 63-72.
27. Stilbs P, Lindman B, Rapacki K. Effect of alcohol cosurfactant length on microemulsion structure. J Colloid Interface Sci., 1983; 95: 583-5.

28. Shafiq-un-Nabi S, Shakeel F, Talegaonkar S. Formulation development and optimisation using nanoemulsion technique: a technical note. AAPS Pharm Sci Tech., 2007; 8: E1-E6.
29. Tiwari NG, Bajaj AN. Formulation development of eucalyptuss oil microemulsion for intranasal delivery. Indian J Pharm Sci., 2007; 69: 731-3.
30. Vyas TK, Babbar AK, Sharma RK, Singh S, Misra A. Intranasal mucoadhesive microemulsions of clonazepam: Preliminary studies on brain targeting. J. Pharm. Sci., 2005; 95: 570-80.
31. Kwatikar PS, kulkarni NP, yadav SP, Sakarkar DM. Formulation and evaluation of an anti-epileptic drug loaded microemulsion for nose to brain delivery. asian J. Pharmaceutics, 2009; 3(2): 143-47.
32. Shende AJ, Patil RR, Devarajan PV. Microemulsion of lomotrigone for nasal delivery. Ind. J. Pharm. Sci., 2007; 69(5): 721-22.
33. Holvoet C, Heyden YV, and Plaizier-Vercammen J. Inclusion complexation of lorazepam with different cyclodextrins suitable for parenteral use. Drug Dev. Ind. Pharm., 2005; 31: 567– 75.
34. Date AA, Nagarsenker MS. Parenteral microemulsions: an overview. Int. J. Pharm., 2008; 355: 19–30.
35. Yalin M, oner F, oner L and Hincal AA. Preparation and properties of a stable intravenous lorazepam emulsion. J. Clin. Pharm. Ther., 1997; 22: 39–44.
36. Amit AK and Vandana BP. Development and evaluation of lorazepam microemulsions for parenteral delivery. AAPS Pharm Sci Tech., 2008; 9(3): 966-71.
37. Pakalnis A, Kring D, Paolicchi J. Parenteral satisfaction with sumatriptan nasal spray in childhood migraine. J Child Neurol, 2003; 18: 772-75.
38. Villalon CM, Centurion D, Valdivia LF, de Vries P, Saxena PR. Migraine: pathophysiology, pharmacology, treatment and future trends. Curr. Vasc. Pharmacol, 2003; 1: 71-84.
39. Martindale PK. The Complete Drug Reference. London, UK: Pharmaceutical Press, 1999: 450-52.
40. Gladstone JP, Gawel M. Newer formulations of the triptans: advances in migraine treatment. Drugs., 2003; 63: 2285-2305.
41. Bigal ME, Bordini CA, Antoniazzi AL, Speciali JG. The triptan formulations: a critical evaluation. Arq. Neuropsiquiatr, 2003; 61: 313-20.

42. Vyas TK, Babbar AK, Sharma RK, Singh S and Misra A. Preliminary Brain-targeting Studies on intranasal mucoadhesive microemulsions of sumatriptan. AAPS Pharm Sci Tech, 2006; 7(1): 8. E1-E9.
43. Shelke R.R. and Devrajan P.V. Aqua triggered In Situ Gelling Microemulsion for Nasal Delivery. Ind. J. Pharm. Sci., Sep-Oct, 2007; 726-27.
44. Tushar K Vyas AK Babbar R, Sharma K and Misra A. Intranasal mucoadhesive microemulsions of zolmitriptan: Preliminary studies on brain-targeting. J. Drug Target, 2005; 13(5): 317-24.
45. Jogani V, Shah P, Mishra P, and Misra AN. Intranasal mucoadhesive microemulsion of tacrine to improve brain targeting. Alzheimer Dis. Assoc. Disord, 2008; 22(2): 116124.
46. Hinchcliffe M, Illum L. Intranasal insulin delivery and therapy. Adv Drug Deliv Rev., 1999; 35: 199–34.
47. Costantino HR., Lisbeth I, Brandt G. Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. International Journal of Pharmaceutics, 2007; 337: 1-24.
48. Sheckler MT, Mermelstein F, Hamilton DA, Carr D (Javelin Pharmaceuticals). Nasal delivery of Analgesics. On Drug Delivery Ltd.2005. Available at: http://www.ondrugdelivery. com.