IJPSR (2013), Vol. 4, Issue 4 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 December, 2012; received in revised form, 21 March, 2013; accepted, 29 March, 2013

AN OVERVIEW ON EXPLORING NASAL MICROEMULSION FOR TREATMENT OF CNS DISORDERS

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Keywords:
Nasal drug delivery, microemulsion, nose to brain transport, drug carrier, target site

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QUICK RESPONSE CODE

IJPSR: ICV (2011)- 5.07

Article can be accessed online on: www.ijpsr.com

ABSTRACT: Nasal route is found to be valuable for targeting drugs to CNS via different mechanisms. The advantages, disadvantages, varius 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. The relevant aspects of physicochemical, formulation and physiological factors of nasal cavity that must be considered during the process of discovery and development of new drugs for nasal delivery drugs as well as in their incorporation into appropriate nasal pharmaceutical formulations are discussed here. There are various approaches in delivering a therapeutic substance to the target site in a controlled release fashion. One such approach is using microemulsion as carriers for drugs. 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. They can be classified as oil-in-water (o/w), water-in-oil (w/o) or bicontinuous systems depending on their structure and are characterized by ultra-low interfacial tension between oil and water phases. Microemulsion received much attention not only for prolonged release, but also for targeting of drugs to a particular site. The intent of the paper is focuses on use of microemulsion technology in drug targeting to the brain along with mechanism of nose to brain transport, formulation and formation of microemulsion and its characterization.

INTRODUCTION:

Intranasal Delivery for Brain Targeting: Nasal drug delivary system used conventionally for local delivary of drugs for treatment of nasal allergies and infections. In recent years research established that the nasal route is safe and acceptable alternate to oral and parentral administration of drugs. Nasal route is found to be valuable for targeting drugs to CNS via different mechanisms [1]. 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. Recently, several nasal formulations, such as ergotamine (Novartis), sumatriptan (GlaxoSmithKline), and zolmitriptan (AstraZeneca) have been marketed to treat migraine. Scientists have also focused their research toward intranasal administration for drug delivery to the brain especially for the treatment of diseases, such as epilepsy [2-7], migraine [8-13], emesis, depression [14] angina pectoris [15] and erectile dysfunction [16].

The treatment of CNS disorders are challenging because of a variety of formidable obstacles for effective and persistent delivery of drugs.

Even though the drugs used for the treatment of CNS disorders are potent, their clinical failure is often not due to lack of drug efficacy but mainly due to short comings in the drug delivery approach. Hence, scientists are exploring the novel approaches so that delivery of the drugs can be enhanced and /or restricted to the brain and CNS.

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 option for brain targeting as brain and nose compartments are connected to each other via olfactory/ trigeminal route via peripheral circulation.

Realization of nose to brain transport and the therapeutic viability of the route can be traced from the ancient times and has been successfully investigated for rapid and effective transport in last two decades. Intranasal drug delivery delivers drug directly to the brain circumventing BBB and reduces drug delivery to the non targeted sites. This may result in reduction in dose, systemic dilution and first pass metabolism of the drug (Illum 2000).

Direct nose to brain transport results into rapid and/ of higher uptake in the brain, which provides an alternative option of self medication in the management of emergencies. However, the development of nasal drug products for brain targeting is facing enormous challenges. For overcoming the obstacles, better understanding in terms of factors which are involved in the direct nose to brain transport (physicochemical factors and formulation factors) and transport mechanisms is of utmost importance. Many sophisticated and effective approaches to the CNS drug delivery have emerged in recent years.

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 [17-19]:

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. 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 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.
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 t_{max} of fentanyl after nasal administration was less than or equal to 7 minute 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 [20-22]:

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. 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 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: 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 [24] that are distinguished according to anatomical and histological structure in **fig. 1 and table 1** along with details given below.

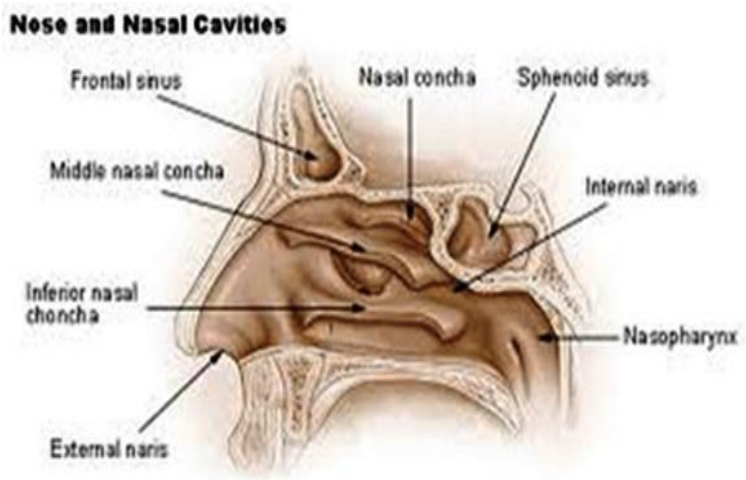


FIG. 1: ANATOMY AND HISTOLOGY OF HUMAN NASAL CAVITY

1. **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 turbinates which are projected from the lateral wall. These specialized 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 [25]. 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.

2. **The olfactory region:** It is of about 10 cm^2 in surface area, and plays a vital role in 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. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons 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 minutes [26]. 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 minutes. Numerous enzymes for instance, cytochrome P450 enzymes, carboxylesterases and glutathione S-transferases are found in nasal cavity [27-29].

3. **The vestibular region**: This is located at the opening of nasal passages and is responsible for filtering out air borne particles. It is considered to be the least important of the three regions with regard to drug absorption.

TABLE 1: HUMAN NASAL EPITHELIUM CHARACTERISTICS:

Nasal Sections	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 - Pseudostratified cells / Support	NF	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

NF- Not Found

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 [30-32]. 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**.

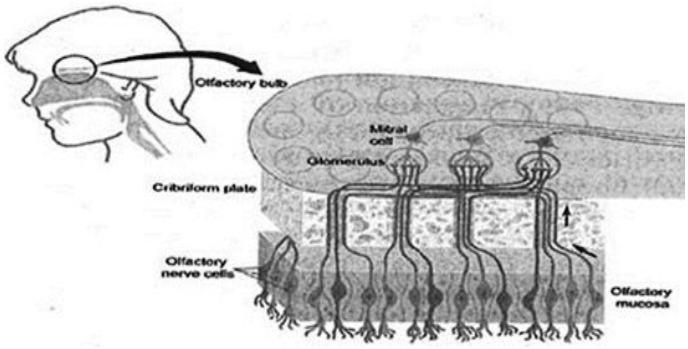


FIG. 2: NOSE TO BRAIN TRANSPORT ROUTES

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 appears to have communications between them. The nasal drug delivery to the CNS is thought to involve either an intraneuronal or extra neuronal pathway [33, 34]. A drug can cross the olfactory path by one or more mechanism/pathways.

These include paracellular transport by movement of drug through interstitial space of cells transcellular or simple diffusion across the membrane or receptor / fluid phase mediated endocytosis and transcytosis by vesicle carrier [35] 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 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 [36, 37] .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 neuron 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 mucosa→ olfactory neurons→ brain and csf	Estradiol
Nasal membrane→ olfactory dendrites→ nervous system→ supporting cells in the olfactory mucosa→ sub mucosal blood vascular system	Norethiandrone Progesterone
Nasal membrane → peripheral circulation and CSF → CNS	Norethisterone
Nasal mucosa→ peripheral and cranial nerves→ CNS	Herpes virus encephalitis
Nasal mucosa→ cranial nerve→ CNS	Herpes virus simplex
Nasopharynx→ cervical lymph	Water

Drug selection properties to penetrate blood-brain/blood-csf barriers [38]:

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

1) **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 [39]. 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. 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 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 & 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.

2) **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 optimize systemic absorption. Nasal irritation is minimized when products are delivered twith a pH range of 4.5 to 6.5. 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 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.

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 unionized 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 formulation. Shrinkage of epithelial cells 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 [41.] Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

d. **Solubilizers**: Aqueous solubility of 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 chainnglycerides and Labrasol can be used to enhance the solubility of drugs[42.] Other options include the use of surfactants or cyclodextrins such as HP-β-cyclodextrin that serve as a biocompatible solubilizer and stabilizer 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 [43].

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 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 & 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 amino peptidases. 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.

3) **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 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 amino-peptidase at the mucosal membrane. The level of amino-peptidase 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 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 reduced

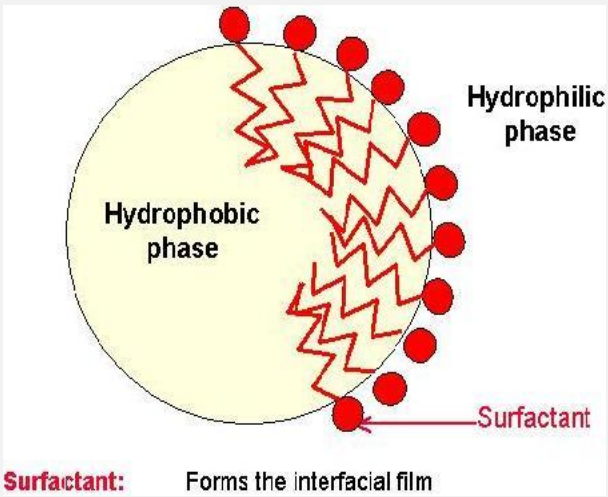
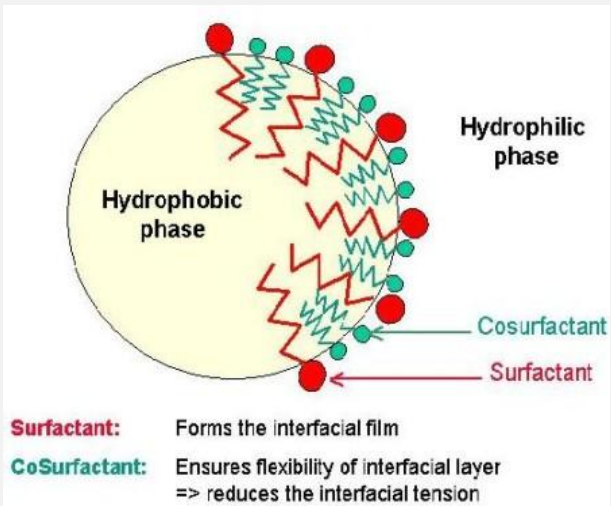
in insulindependent diabetes. Nasal pathology can also alter mucosal pH and thus affect absorption.

Micro emulsions as a Drug Delivery System for Brain Targeting: Emulsions are 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 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, where as 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 [44]. 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" [45]. The difference between appearance of emulsion and microemulsion given in **fig. 3 and table 3**.

FIG. 3: DIFFERENCE BETWEEN APPEARANCE OF EMULSION AND MICROEMULSION

TABLE 3: SHOWING DIFFERENCE BETWEEN EMULSION AND MICROEMULSION [46-51]

Emulsion (Macroemulsion)	Microemulsion
 **Emulsion**	 **Microemulsion**
Emulsion consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
Droplet diameter: 1 – 20 mm.	10 – 100 nm.
Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.

Ordinary emulsion droplets, however small exist as individual entities until coalesance or ostwald ripening occurs.	Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than macroemulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
They are lyophobic.	They are on the borderline between lyophobic and lyophilic colloids.
Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients.

Types of microemulsion: 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 [52]

Why Microemulsion is prefered over other dosage forms: In recent years microemulsions have attracted a great deal of attention because of their following advantages:

1. Ease of manufacturing and scale-up.
2. Wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
3. Helps in solubilization of lipophillic drug hence Increase the rate of absorption and bioavailability of drugs.
4. Eliminates variability in absorption.
5. Provides a aqueous dosage form for water insoluble drugs.
6. Various routes like tropical, oral and intravenous can be used to deliver the drugs [53]
7. Rapid and efficient penetration of the drug moiety.
8. Helpful in taste masking.
9. Same microemulsions can carry both lipophilic and hydrophilic drugs.
10. Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.
11. Liquid dosage form increases patient compliance.
12. Less amount of energy requirement.
13. Microemulsion lower the skin irritation: alcohol-free microemulsions have been reported with much lower irritation potential.
14. Long shelf life as compared to other colloidal drug delivery system.
15. High drug loading.
16. Improve therapeutic efficacy of drugs and allow reduction in the volume of the drug delivery vehicle, thus minimizing toxic side effects [54].
17. Easy to administer in child and adults who have difficulty swallowing solid dosage forms.

Why Microemulsions are chosen for Nose 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: The main problem in a microemulsion application is a high concentration and a narrow range of physiologically acceptable surfactants and co-surfactants [55, 56]. Large surfactant concentration (10-40%) determines their stability [57]. Selection of components: if the systems are to be used topically, selection of components involves a consideration of their toxicity, irritation and sensitivity [58].

Nasal congestion due to cold or allergies may interfere with absorption of drug through nasal mucosa. Delivery is expected to decrease with increasing molecular weight of 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. Fluidity of interfacial film should be low to promote the formulation of microemulsion [59].

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.

1) **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) [60]. Saturated (for example, lauric, myristic and capric acid) and unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) have penetration enhancing 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.

2) **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, where as 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.

3) **Cosurfactants** : In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form [61-63]. 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 [64-66]. 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:

1. **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, pseudo ternaryphase 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* [67] (Fig. 4).

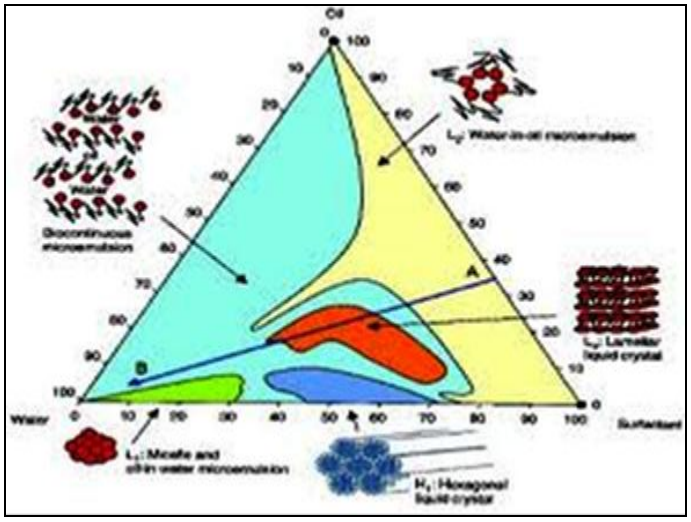


FIG. 4: PSEUDO TERNARY PHASE DIAGRAM OF OIL, WATER AND SURFACTANT SHOWING MICROEMULSION REGION.

2. **Phase Inversion Method:** Phase inversion of microemulsions occurs upon addition of 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 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 stabilizing 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.

Factors affecting the Microemulsion [68]: The formation of microemulsion will depend on the following factors:

1. **Packing ratio**: The HLB of surfactant determines the type of microemulsion through its influence on molecular packing and film curvature. The analysis of film curvature for surfactant association's leadings to the formation of microemulsion.

Critical packing ratio is given by:

C.P.P. (Critical Packaging Parameters) = V / (a × l)

Where, V = volume of surfactant molecule

a = head group surface area l = length

If c.p.p is between 0-1, interface curves towards water (positive)

If c.p.p is greater than 1, interface curves towards oil (negative)

If c.p.p is equal to 1, then either bicontinuous or lamellar structure.

2. **Property of surfactant, oil phase and temperature**: The type of microemulsion depends on the nature of surfactant. Surfactant contains hydrophilic head group and lipophilic tail group. The areas of these group, which are a measure of the differential tendency of water to swell head group and oil to swell the tail area are important for specific formulation when estimating the surfactant HLB in a particular system. When a high concentration of the surfactant is used or when the surfactant is in presence of salt, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type.

   Diluting with water may increase dissociation and leads to an o/w system. Ionic surfactants are strongly influenced by temperature. It mainly causes increased surfactant counter-ion dissociation. The oil component also influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chains oils penetrate the lipophilic group region to a great extent and results in increased negative curvature. Temperature is extremely important in determining the effective head group size of nonionic surfactants. At low temperature, they are hydrophilic and form normal o/w system. At higher temperature, they are lipophilic and form w/o systems. At an intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuous structure.

3. **The chain length, type and nature of cosurfactant**: Alcohols are widely used as a cosurfactant in microemulsions. Addition of shorter chain cosurfactant gives positive curvature effect as alcohol swells the head region more than tail region so, it becomes more hydrophilic and o/w type is favoured, while longer chain cosurfactant favours w/o.

Evaluation of Microemulsions: The microemulsions are evaluated by the following techniques.

1. **Phase behavior studies**: Visual observations, phase contrast microscopy and freeze fracture transmission electron microscopy can be used to differentiate microemulsions from liquid crystals and coarse emulsions. Clear isotropic one-phase systems are identified as microemulsions whereas opaque systems showing bifringence when viewed by cross polarized light microscopy may be taken as liquid crystalline system.

2. **Rheology**: Change in the rheological characteristics help in determining the microemulsion region and its separation from other related structures like liquid crystals. Bicontinuous microemulsion are dynamic structures with continuous fluctuations occurring between the Bicontinuous structure, swollen reverse micelle, and swollen micelles.

3. **Scattering Techniques**: Scattering techniques such as small angle neutron scattering, small angle X-ray scattering and light scattering have found applications in studies of microemulsion structure, particularly in case of dilute monodisperese spheres, when polydisperse and/or concentrated systems such as those frequently seen in microemulsions.

4. **Dynamic light-scattering measurements** [69-72] :The DLS measurements are taken at 90° in a dynamic light-scattering spectrophotometer which uses a neon laser of wavelength 632 nm. The data processing is done in the built-in computer with the instrument.

5. **Polydispersity**: This property is characterized by Abbe refractometer.

6. **Interfacial tension**: Spinning-drop apparatus can be used to measure the ultralow interfacial tension.

Application of Microemulsion in Brain Targeting: Intranasal administration confers a simple, economic, convenient and noninvasive route for rapid drug delivery to systemic circulation:

1) **Treatment of Epilepsy and schizophrenia**: Vyas *et al*., prepared mucoadhesive microemulsion for the antiepileptic drug clonazepam [73]. 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*., prepared microemulsion containing valproic acid showed a fractional diffusion efficiency and better brain bioavailability efficiency [74] Hence microemulsions are the promising approach for delivery of valproic acid to the brain for treatement of epilepsy.

Florence *et al*., prepared clobazam microemulsion and mucoadhesive microemulsion. Formulations were assessed for the average onset of seizures in pentylene tetrazole treated mice. This study demonstrated high brain targeting efficiency of prepared clobazam mucoadhesive microemulsion and delayed onset of seizures induced by pentylene tetrazole in mice after intranasal administration of developed formulation [75.] 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 quick onset of action in case of emergency in epilepsy [76].

Lorazepam (LZM) is a poorly water-soluble drug which can be used as tranquillizer, muscle relaxant, sleep inducer, sedative and antiepileptic agent [77]. 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 [78].

Furthermore, parenteral administration of the organic co-solvents can also cause hemolysis [79]. Amit *et al*., 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 [80].

2) **Treatment of migraine**: Migraine treatment has evolved in the scientific arena, and opinions differ on whether migraine is primarily a vascular or a neurological dysfunction [81]. Sumatriptan is rapidly but incompletely absorbed following oral administration and undergoes first-pass metabolism, resulting in a low absolute bioavailability of 14% in humans [82.] The transport of Sumatriptan across the blood-brain barrier (BBB) is very poor [83.] Studies have demonstrated that intranasal administration offers a practical, noninvasive, alternative route of administration for drug delivery to the brain [84, 85].

   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 maximize the therapeutic index [86].

   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 treatment of migraine [87]. 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].

3) **As an antidepressant**: Tiwari *et al*., developed eucalyptus oil microemulsion for intranasal delivery to the brain [89]. 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.

4) **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 the 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.

5) **Treatment of amnesia**: 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 scopolamine-induced amnesic mice [92]. 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.

6) **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. Some intranasal non peptides and peptides available in market are listed in **table 4 and 5** [93, 94].

TABLE 4: EXAMPLES OF (NON PEPTIDE) NASAL FORMULATIONS COMMERCIALLY AVAILABLE FOR SYSTEMIC DRUG DELIVERY AFTER PRESCRIPTION

Drug	Brand	Main Excipients	Supplier	Main Indications	Dosage form
Zolmitriptan	Zomig Nasal Solution (spray)	Citric acid, disodium phosphate dodecahydrate	AstraZeneca	Treatment of migraine and cluster headache	Solution (spray)
Sumatriptan	Imigran solution (spray)	Potassium dihydrogen phosphate, dibasic sodium phosphate anhydrous	GlaxoSmithKline	Treatment of migraine and cluster headache	Solution (spray)
Estradiol	Aerodiol	Methylbetadex, sodium Chloride	Servier laboratories	Hormone replacement therapy	Solution (spray)

TABLE 5: EXAMPLES OF (PEPTIDE) NASAL FORMULATIONS COMMERCIALLY AVAILABLE FOR SYSTEMIC DRUG DELIVERY AFTER PRESCRIPTION

Drug	Brand	Main Excipients	Supplier	Main Indications	Dosage form
Oxytocin	Syntocinon	Citric acid, chlorobutanol, sodium chloride	Novartis	Lactation Stimulation	Solution (spray)
Salmon Calcitonin	Miacalcin	Sodium chloride, benzalkonium chloride, hydrochloric acid	Novartis	Treatment of postmenopausal osteoporosis	Solution (spray)
Buserelin (Profact nasal)	Suprefact	Sodium hydroxide, sodium chloride, sodium dihydrogen phosphate	Sanofi-Aventis	Treatment of prostate cancer	Solution (spray)
Nafarelin	Synarel	Benzalkonium chloride, glacial acetic acid	Roche Laboratories	Management of endometriosis	Solution (spray)

7) **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. Some nasal vaccinations available in market are listed below in **table 6**.

TABLE 6: NASAL DRUG PRODUCT FOR VACCINATION AVAILABLE IN THE MARKET

Vaccine (Product name)	Dosage form	Status	Manufacturer
Human influenza vaccine (Nasalflu Berna)	Virosomes (Spray)	Marketed (withdrawn)	Berna Biotech
Equine influenza vaccine (Flu Avert)	Drops	Marketed	Heska
Porcine Bordetella bronchiseptica vaccine(Maxi/ Guard Nasal Vac)	Drops	Marketed	AddisonBiological Laboratory
Feline Bordetella bronchiseptica vaccine (Nobivac Bp)	Suspension drops	Marketed	Intervet
Human Streptococcus A vaccine (StrepAvax)	Proteosomes (nanoparticulate)	Phase 2	ID Biomedical
Human influenza vaccine (FluINsuru)	Proteosomes (nanoparticulate)	Phase 2	ID Biomedical
Human influenza vaccine	Not indicated.	Phase 1/2	West PS
Human influenza vaccine (FluMist)	Spray	Marketed	Medlmmune Inc.
Feline trivalent vaccine against calici herpes-1and parvovirus	Drops	Marketed	Heska

8) **Intranasal delivery of Analgesics** [95]: 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.

Patents on Microemulsion: During the last one decay much research work has been done on microemulsions for various routes of drug administration. Due to their unique properties namely, ultraflow interfacial tension, large interfacial area, thermodynamic stability and the ability to solubilize otherwise immiscible liquids. There are very few microemulsions are patented some of them are listed below in **table 7**.

TABLE 7 : SHOWING SOME PATENTED MICROEMULSION FORMULATIONS

Cited Patent	Filing date	Issue date	Original Assignee	Title
US4472291	Mar 7, 1983	Sep 18, 1984		High viscosity microemulsions
US4536323	Jun 28, 1983	Aug 20, 1985	The Drackett Company	Non-flammable aerosol propellant microemulsion system
US5266590	Nov 19, 1992	Nov 30, 1993	ISP Investments Inc.	Cold stabilization of aqueous microemulsions of a water-insoluble agriculturally active compound
US5385948	Feb 16, 1993	Jan 31, 1995	ISP Investments Inc.	Alkoxyalkyl lactams as solvents for macro and microemulsions.
US5389297	Jun 9, 1993	Feb 14, 1995	ISP Investments Inc.	Inert matrix composition microemulsifiable concentrate and aqueous microemulsion
US5389688	Mar 30, 1993	Feb 14, 1995	Isp Investments Inc.	Water based microemulsion formulations
US5444078	Oct 1, 1993	Aug 22, 1995	Rohm and Haas Company	Fully water-dilutable microemulsions
US6531144	Jul 22, 2002	Mar 11, 2003	Dainihon Jochugiku Co., Ltd.	Microemulsion aerosol composition
US6703034	Dec 10, 2001	Mar 9, 2004	University of Florida	Neem oil microemulsion without cosurfactants or alcohols and a process to form the same

CONCLUSION: Microemulsions are optically isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. Microemulsions are readily distinguished from normal emulsions by their transparency, low viscosity and more fundamentally their thermodynamic stability. Drug delivery through microemulsions is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability and for drug targeting to various sites in the body.

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How to cite this article:
Vispute M., Nazim S., Khan T. and Shaikh S: An overview on exploring Nasal Microemulsion for treatment of CNS disorders. *Int J Pharm Sci Res* 2013; 4(4); 1294-1311.