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Microemulsion as A Carrier for Intranasal Drug Delivery System

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ABSTRACT

The novel carriers have been exploited through almost all the routes of administration. Many newer carriers are evolving with the advent of technology and the demand of targeted delivery like microemulsions. Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant. These systems are currently of interest because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules. In addition to oral and intravenous delivery, they are amenable for sustained and targeted delivery through nasal, pulmonary, vaginal and topical routes. The intent of the paper focuses on use of microemulsion technology in intranasal drug delivery along with mechanism.

Keywords: Microemulsion, Intranasal, Drug delivery system

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INTRODUCTION

The design and development of new drug delivery system with the intention of enhancing the efficacy of existing drug is ongoing process in pharmaceutical research. It is necessary for a pharmaceutical solution to contain a therapeutic dose of the drug in a volume convenient for administration. Of the many types of drug delivery system that have been developed, one is, the colloidal drug delivery system which has great potential for achieving the goal in drug targeting. Colloidal drug delivery systems are used to increase the bioavailability of drug substances, to improve drug stability, to sustain and control drug-release rates, to target drugs to specific sites in the body, and to stimulate the immune system[1]. Microemulsions as colloidal carriers are one of the promising systems which now a day attracted the main interest in colloidal drug delivery system.

Microemulsions are liquid dispersions of water and oil that are made homogenous, transparent or translucent and thermodynamically stable by the addition of relatively large amounts of a surfactant and a co-surfactant and having diameter of the droplets in the range of 10 – 100 nm[2-6]. Microemulsions have been widely studied for drug targeting to the brain and to enhance the bioavailability of the poorly soluble drugs[7]. Microemulsions have very low surface tension and small droplet size which results in high absorption and permeation. Interest in these versatile carriers is increasing and their applications have been diversified to various administration routes in addition to the conventional oral route. This can be attributed to their unique solubilization properties and thermodynamic stability which has drawn attention for their use as carrier for nasal drug delivery system.

Microemulsions, by virtue of its lipophilicity and low globule size, are explored widely as a delivery system to enhance uptake across nasal mucosa. Intranasal drug delivery system must be meticulously designed to provide rapid transport of drug across nasal mucosa and longer residence time in nasal cavity.

Literature survey revealed that intranasal administration of microemulsion offers a practical, noninvasive technique for direct nose to CNS drug delivery[8-10]. This drug delivery route works because of the unique neuronal connection which the trigeminal and olfactory nerves provide between the nasal cavity and the cerebrospinal fluid and brain. Also, microemulsions are suitable carriers for drugs susceptible to hydrolysis in aqueous medium. Therefore, particularly intranasal microemulsions are promising carrier for achieving the goals in drug targeting to brain.

Intranasal Drug Delivery System

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 com-pounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents[11]. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA"[12]. Nasal drug delivery which has been practiced for thousands of years has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show minimal oral bioavailability such as proteins and peptides. The nasal route circumvents hepatic first pass elimination associated with the oral delivery. During the past several decades, the feasibility of drug delivery via the nasal route has received increasing attention from pharmaceutical scientists and clinicians. Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models. It has been documented that nasal administrations of certain hormones and steroids have resulted in a more complete absorption. This indicates the potential value of the nasal route for administration of systemic medications as well as utilizing this route for local effects[13].

Advantages[11, 14]

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. 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 gastrointestinal tract (GIT) fluids are given by nasal route.
10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

Limitations[15, 16]

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

Anatomy & physiology of nasal cavity

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. The nasal cavity consists three main regions are nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarges about 150cm by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinates: the superior, the median and the inferior[17]. The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrows structures are useful to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; non olfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport[18]. In this way the mucus layer is propelled in a direction from the anterior to-wards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mucus as mucus granules which swell in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulin, lysozyme and lactoferrin, and 1% lipids[19]. The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions. (1) It covers the mucosa, and physically and

enzymatically protects it. (2) The mucus has water holding capacity. (3) It exhibits surface electrical activity. (4) It permits efficient heat transfer. (5) It acts as adhesive and transports particulate matter towards the nasopharynx[20].

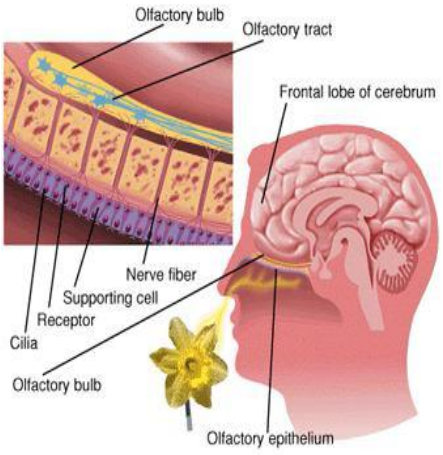

Figure 1: Nasal mucosa

Mechanism of nasal absorption[21]

1. First mechanism

It involves an aqueous route of 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. Drugs having the molecular weight greater than 1000 Daltons show poor bioavailability.

2. Second mechanism

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

Microemulsions as Intranasal Drug Delivery

In 1959, Schulman *et al*. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions"[22]. 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. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity.

Microemulsions as drug delivery tool show favourable properties like thermodynamic stability (long shelf-life), easy formation (zero interfacial tension and almost spontaneous formation),

optical isotropy, ability to be sterilized by filtration, high surface area (high solubilization capacity) and very small droplet size. The small droplets also provide better adherence to membranes and transport drug molecules a controlled fashion. Microemulsions are easy to administer to children and to people who have difficulty swallowing solid oral dosage forms.

Types of microemulsion systems:

According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are referred as Winsor phases [23, 24]. They are,

1. **Winsor I:** With two phases, the lower (o/w) microemulsion phases in equilibrium with the upper excess oil.
2. **Winsor II:** With two phases, the upper microemulsion phase (w/o) microemulsion phases in equilibrium with lower excess water.
3. **Winsor III:** With three phases, middle microemulsion phase (o/w plus w/o, called bicontinous) in equilibrium with upper excess oil and lower excess water.
4. **Winsor IV:** In single phase, with oil, water and surfactant homogenously mixed.

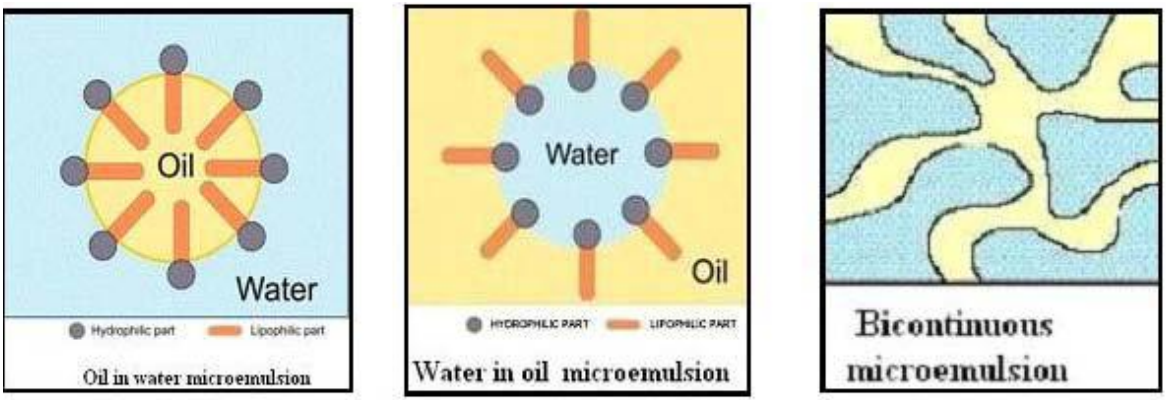

Figure 2: Types of Microemulsions

Advantages of microemulsion over other dosage form

- Increase the rate of absorption
- Eliminates variability in absorption
- Helps solublize lipophilic drug[25]
- Provides an aqueous dosage form for water insoluble drugs
- Increases bioavailability
- Various routes like tropical, oral and intravenous can be used to deliver the product
- Rapid and efficient penetration of the drug moiety
- Helpful in taste masking
- Provides protection from hydrolysis and oxidation as drug in oil phase in o/w

microemulsion is not exposed to attack by water and air.

- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.

Role of Microemulsion in Nasal Drug Delivery

An intranasal microemulsion is one of the focused delivery options for noninvasive drug delivery to systemic circulation[26]. In addition with mucoadhesive polymer helps in prolonging residence time on the mucosa[27]. Microemulsion lower the skin irritation: alcohol-free microemulsions have been reported with much lower irritation potential. The small droplets also provide better adherence to membranes and transport drug molecules in a controlled fashion.

Challenges in nasal drug delivery via microemulsion

1. The main problem in a microemulsion application is a high concentration and a narrow range of physiologically acceptable surfactants and co-surfactants[28, 29].
2. Large surfactant concentration (10-40%) determines their stability[30].
3. Selection of components: if the systems are to be used topically, selection of components involves a consideration of their toxicity, irritation and sensitivity[31].
4. Nasal congestion due to cold or allergies may interfere with absorption of drug through nasal mucosa.
5. Delivery is expected to decrease with increasing molecular weight of drug.
6. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.
7. Concentration achievable in different regions of the brain and spinal cord varies with each agent.
8. Fluidity of interfacial film should be low to promote the formulation of microemulsion.

Components of microemulsion formulations

A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsions. The emphasis is, therefore, on the use of generally regarded as safe (GRAS) excipients.

Oil Phase

The oil component influences curvature by its ability to penetrate and swell the tail group region

of the surfactant monolayer. Following are the different oil is mainly used for the formulation of microemulsion[32]:

I. Saturated fatty acid. Example: lauric acid, myristic acid, capric acid.
II. Unsaturated fatty acid . Example oleic acid, linoleic acid, linolenic acid.
III. Fatty acid ester. Example: ethyl or methyl esters of lauric, myristic and oleic acid.

Aqueous phase

The aqueous phase may contain hydrophilic active ingredients and preservatives. Buffer solutions are used as aqueous phase by some researchers.

Surfactnts[28,29]

The role of surfactant in the formulation of microemulsion is to lower the interfacial tension which will ultimately facilitates dispersion process during the preparation of microemulsion and provide a flexible around the droplets. Generally, low HLB surfactants are suitable for w/o microemulsion, whereas high HLB (>12) are suitable for o/w microemulsion. Following are the different surfactants are mainly used for microemulsion.

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

Cosurfactants[33]

Cosurfactants are mainly used in microemulsion formulation for following reasons:

- They allow the interfacial film sufficient flexible to take up different curvatures required to form microemulsion over a wide range of composition.
- Short to medium chain length alcohols (C_3-C_8) reduce the interfacial tension and increase the fluidity of the interface.
- Surfactant having HLB greater than 20 often require the presence of cosurfactant to reduce their effective HLB to a value within the range required for microemulsion formulation.

Following are the different cosurfactant mainly used for microemulsion:

sorbitan monoleate, sorbitan monosterate, propylene glycol, propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy)ethanol (Transcutol) and ethanol.

Preparation of microemulsion

Following are the different methods are used for the preparation of microemulsion:

Phase titration method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method)

and can be 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 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 as shown in Figure. 3.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[34].

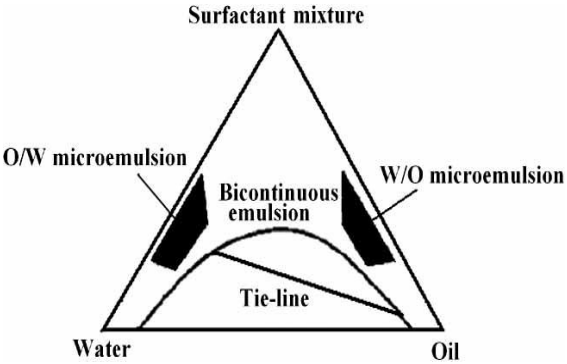

Figure 3. Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region

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.

APPLICATION OF MICROEMULSION IN NASAL DRUG DELIVERY SYSTEM

Intranasal micoremulsions have been reported to provide a noninvasive technique for direct nose to CNS drug delivery and a mucoadhesive microemulsion consisting of mucoadhesive polymer provides prolonged residence in the nasal. It is desirable to achieve rapid and complete absorption of drugs. Also, microemulsions are suitable carriers for drugs susceptible to hydrolysis in aqueous medium

1. Treatment of Migraine:

Migraine attack is troublesome physiological condition associated with throbbing intense headache in one half of the head. Sumatriptan succinate (SS), triptan derivatives are serotonin agonist (5HTD1) used in the treatment of migraine. Migraine patients not only suffer from gastric stasis but also have severe nausea and vomiting, which results in erratic absorption of SS from GIT. Low oral bioavailability of sumatriptan succinate (15%) due to high first pass metabolism justifies a need of nasal drug delivery.

Vyas *et al*[35] 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.

Mahajan *et al*[36] prepared sumatriptan succinate mucoadhesive microemulsion, which was suitable for intranasal delivery. Nasal absorption of sumatriptan succinate from this mucoadhesive microemulsion was found to be fairly rapid, as it converts into gel inside the nasal cavity and increase the residence time and could improve bioavailability of the drug. The result suggests that this mucoadhesive microemulsion may be a useful approach for the rapid onset delivery of sumatriptan succinate during the emergency treatment of acute attack of migraine.

Shelke *et al*[37] has reported that Zolmitriptan microemulsion from nose to brain delivery provide

the dual advantages of enhanced bioavailability with rapid onset of action in treatment of migraine.

Tushar *et al*[38] has investigated zolmitriptan microemulsions (ZMME) 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 ZMME and can play a promising role in the treatment of acute attacks of migraine.

Darshana *et al*[39] prepared winsor type III microemulsion formulations containing peppermint oil and eucalyptus oil for complementary treatment of migraine. Peppermint oil formulations were found to be better for complementary treatment of migraine compared to marketed and eucalyptus oil containing formulations. However, all the developed formulations can be used for their antimigraine activity. The intranasal spray of peppermint oil is a cost effective formulation as the excipients used are easily available. Also, it is an efficient formulation which provides rapid onset of action and complementary treatment of migraine.

Gargi *et al*[40] formulated a novel 'polymer free' microemulsion based aqua triggered in situ (ATIS) gelling drug delivery system of sumetriptan succinate. ATIS gel was formulated by using tween 80, capmul MCM and propylene glycol. Sumetriptan succinate loaded microemulsion based ATIS gel showed good sprayability and rapid gelling when dropped on a moist surface. High retention time in rabbit nasal mucosa was evaluated by the potential of ATIS gel of sumetriptan succinate as an effective nasal drug delivery system.

2. Treatment of Epilepsy and schizophrenia:

Vyas *et al*[41] prepared mucoadhesive microemulsion for an 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 intravenous was found to be 2-fold higher indicating larger extent of distribution of the drug in the brain.

Surjyanarayan *et al*[42] prepared mucoadhesive microemulsion containing Carbamazepine to enhance the aqueous solubility and to accomplish the intranasal delivery of Carbamazepine to brain. This study revealed that mucoadhesive microemulsion containing Carbamazepine showed 17.6% higher drug release than that of plain drug solution of Carbamazepine.

Kwatikar *et al*[43] prepared microemulsion containing valproic acid showed a fractional diffusion efficiency and better brain bioavailability. Hence microemulsions are the promising approach for delivery of valproic acid to the brain for treatment of epilepsy.

Florence *et al*[44] has 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. However, clinical evaluation of the developed formulation may result into 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*[45] prepared microemulsion of lomotrigone from nose to brain delivery. Intranasal administration allows transport of the drug to the brain circumventing blood brain barrier, thus providing the better option to target drug to the brain with quick onset of action in case of emergency in epilepsy.

Botner *et al*[46] prepared a new alcohol-free microemulsion system as a carrier for diazepam or midazolam given intranasally The nasal absorption of both drugs from the same microemulsion formulation (containing 20% aqueous phase) was found to be fairly rapid after administration of 0.4 mg/kg to rabbits. This result suggested that the new microemulsion system may be useful for getting rapid onset of midazolam and diazepam following intranasal administration, resulting in reasonable peak plasma levels and bioavailability, but most importantly, providing a high measure of tolerability and comfort.

Shahiwala *et al*[47] developed intranasal microemulsions of Zonisamide (ZNS) for direct brain drug delivery. The results of the present investigation suggest that the developed microemulsion system is a promising approach for effective intranasal delivery of ZNS which can enhance its brain delivery for successful treatment of epilepsy.

Kamla *et al*[48] formulated Risperidone nanoemulsion (NE) and mucoadhesive NE formulations by the spontaneous emulsification method (titration method) using Capmul MCM as the oily phase on the basis of solubility studies. The nanoemulsion formulations had a globule size of 15.5±2.12 nm and polydispersity of 0.172±0.02. The mucoadhesive formulation that contained 0.5% by weight of chitosan displayed highest diffusion coefficient that followed Higuchi model.

Misra *et al*[49] prepared nanoemulsion containing risperidone. Risperidone nanoemulsion and mucoadhesive nanoemulsion were characterized for drug content, pH, percentage transmittance, globule size and zeta potential. Gamma scientigraphy imagine of rat brain following i.v. and i.m. administrations were performed to ascertain the localization of drug in brain. Higher drug

transport efficiency (DTE %) and direct nose to brain drug transport (direct transport percentage) for mucoadhesive nanoemulsion indicated more effective and best brain targeting.

3. As an Antidepressant:

Tiwari *et al*[50] has developed Eucalyptus oil microemulsion for intranasal delivery to the brain. This work demonstrated that the microemulsion of eucalyptus oil is cost effective and efficient formulation which provides the rapid onset in soothing stimulant and antidepressant action

Amrish *et al*[51] prepared micremulsions containing sertraline Hydrochloride for intranasal delivery to accomplish rapid onset of action. It suggested that intranasal microemulsion of sertraline hydrochloride may be beneficial for the treatment of depression.

4. **Treatment of angina Pectoris and neurological deficit**:

Qizhi Zhang *et al*[26] has prepared the microemulsion to improve the solubility and enhance the brain uptake of nimodipine, which was suitable for intranasal delivery. The uptake of nimodipine 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 nimodipine, for the treatment and prevention of neurodegenerative diseases.

Jing Yao *et al*[52] has prepared hyaluronic acid chitosan based microemulsion (HACME) containing nobiletin and determines its distribution in mice brain following i.v. administration. Based on AUC_{0-t}, MRT and C_{max}, HACME delivered more nobiletin to the brain compared to nobiletin solution. These results indicate that HACME may be presented as potential candidates for delivering more drugs into the brain.

5. Treatment of Amnesia:

Jogani *et al*[53] has studied microemulsion /mucoadhesive micromulsion of tacrine, assessed its pharmacokinetic and pharmacodynamic performances for brain targeting and for improvement in memory in scopolamine induced 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.

6. Treatment of hyperprolactinemia:

Gitanjali *et al*[54] prepared and characterized cabergoline intranasal microemulsion formulations, and determined brain drug delivery through biodistribution using technetium-99_m (99_mTc) as a tracer, and assessed its performance pharmacodynamically in weight control. The results of the studies conclusively demonstrated that intranasal microemulsion formulations developed in this

investigation can deliver cabergoline selectively and in higher amounts to the brain compared to both drug administrations as a solution intranasally or microemulsion intravenously.

7. Erectile dysfunction:

Ahmed *et al*[55] prepared intranasal delivery system of sildenafil citrate and estimate its relative bioavailability after nasal administration in rabbits. The prepared systems were characterized in relation to their clarity, particle size, viscosity, pH, and nasal ciliotoxicity. *In vivo* pharmacokinetic performance of microemulsion was evaluated in a group of six rabbits in a randomized crossover study and compared to the marketed oral tablets. Microemulsion formulation showed shorter t_{max} (0.75 h) and higher AUC $_{(0-\infty)}$ (1,412.42 ng h/ml) compared to the oral tablets. The result of the study demonstrated that nasal absorption of sildenafil citrate microemulsion was found to be fast, indicating the potential of nasal delivery instead of the conventional oral administration of such drug.

Hyun-Jong cho *et al*[56] et al developed a microemulsion system of udenafil for its nasal drug delivery system. Microemulsions were prepared by various ratios of capmul MCM L8 as oil, labrasol as a surfactant, and transcutol or its mixture with ethanol (1:0.25 v/v) as a cosurfactant. An *in vitro* permeation study was performed in human nasal epithelial cell monolayers cultured by the air-liquid interface method. The result demonstrated that udenafil-loaded microemulsion had a shorter T_{max} value compared with oral administration and improved bioavailability (85.71%) compared with oral and intranasal solution.

8. Insulin delivery:

Amnon *et al*[57] prepared microemulsion spray preparation of insulin. The bioavailability of insulin lispro via the nasal route using a W/O microemulsion was found to reach 21.5% relative to subcutaneous administration. The profile of plasma glucose levels obtained after nasal spray application of the microemulsion (1 IU/kg lispro) was similar to the subcutaneous profile of 0.5 IU/kg at the first 90 min after application and resulted in a 30–40% drop in glucose levels. The effect of the microemulsion on fluorescein isothiocynate insulin (FITC)-labeled insulin permeation was examined across the porcine nasal mucosa *in vitro*. The result concluded that the acceleration in the intramucosal transport process is the result of encapsulating insulin within the nano-droplet clusters of a W/O microemulsion, while the microemulsion ingredients seems to have no direct role.

Amnon *et al*[58] prepared a microemulsion using labrasol, glyceryl oleate, isopropyl palmitate and propylene carbonate. They studied the feasibility of increasing brain insulin levels by intranasal administration of insulin in microemulsion form. They showed that the intranasal administration

of fluorescently labeled insulin (FITC-insulin) in w/o microemulsion to rats resulted in a significantly higher brain labeling compared with the aqueous solution as measured using quantitative image analysis. Higher uptake of FITC-insulin into the brain was noted with intranasal administration via microemulsion, is of great potential to targeting insulin to the brain in patient with neurological disorders, such as alzheimer disease.

CONCLUSION

Microemulsion are commercially feasible , simple and convenient vehicles for delivery of medicaments which can enhance the drug absorption with reduced systemic side effects. Intranasal drug delivery system is a promising alternative route of administration for poor bioavailability drugs and it has advantages in term of increase patient acceptability and compliance. So, an intranasal microemulsion is one of the important delivery system for noninvasive drug delivery to systemic circulation.

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