Microemulsions for Nasal Drug Delivery Systems: An Overview

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ABSTRACT
Most drugs cannot be given orally because of significant degradation in the GIT or first pass metabolism in the liver. Nasal route for the delivery of some drugs offers an alternative in the pharmaceutical industry. The present review deals with the utility of the nasal route for the delivery of drugs to the brain as a microemulsion system in the treatment of a number of ailments like migraine, epilepsy, and hypertension. The nasal route could be important for drugs that are used in crisis treatments, such as for pain, and for centrally acting drugs where the pathway from nose to brain might provide a faster and more specific therapeutic effect. The purpose of the article is to provide an overview of the concept of microemulsion, selection of surfactant, co-surfactant, oils, formulation of microemulsion, phase diagram study, and evaluation of microemulsion. The review also focuses on the excipients available for formulation of microemulsions for nasal delivery and describes the investigations reported for the various classes of therapeutic agents. The interesting features of microemulsion such as spontaneity of formation, ease of manufacturing, high solubilization capacity and self-preserving properties make them the vehicle of choice for nasal delivery.

KEYWORDS: Microemulsion; nasal delivery; mucoadhesion; drug delivery; solubilization.

Introduction
Nasal drug delivery is increasingly important as an alternative to the oral and parenteral routes for systemic drug delivery. There has been increasing interest in using the nose as a route for administration of systemically active drugs. There are number of research and review articles on nasal drug delivery. This interest arises from the different possible advantages presented by the nasal cavity such as: vascularized epithelium, large surface area available for drug absorption, lower enzymatic activity compared to the gastrointestinal tract and liver and the direct transport of absorbed drugs into the systemic circulation, thereby, avoiding hepatic first-pass metabolism and irritation of gastrointestinal membrane. Also, the nasal route is non-invasive, therefore produces reduced risk of infection, ease of convenience and self medication resulting in improved patient compliance (Ugwoke et al., 2001). Although nasal administration of drugs has many disadvantages, one of the most important is the nasal mucociliary clearance that limits the time allowed for drug absorption to occur (Martinac et al., 2005). To overcome the rapid clearance mainly two approaches have been utilized. Use of penetration enhancers (surfactants, bile salts, cyclodextrins, phospholipids and fatty acids), which can promote the absorption of poorly absorbable drugs and use mucoadhesive systems (bioadhesive liquid formulations, mucoadhesive microemulsion, microspheres, powders and liquid gelling formulations) that decrease the mucociliary clearance of drug formulation and thereby increase the contact time between the drug and the site of absorption. The world market has seen an increasing number of systemically acting drugs being marketed as nasal formulation, including a range of anti-migraine drugs such as sumatriptan from GlaxoSmithKline, zolmitriptan from AstraZeneca, ergotamine from Novartis and butorphanol from BristolMyersSquibb, as well as a range of peptides, such as calcitonin marketed by Novartis, desmopressin from Ferring and buserelin from Aventis (Majithiya et al., 2006). Intranasal drug delivery also offers advantages such as drugs being able to be administered simply, cost effectively, and conveniently (Liu et al., 2001). Direct transport of drugs to the brain circumventing the brain-barriers following intranasal administration provides a unique feature and better option to target drugs to the brain (Lisbeth, 2003; Vyas et al., 2005).

Microemulsions, by virtue of their lipophilic nature and low globule size, are widely explored as a delivery system to enhance uptake across mucosa (Hu et al., 2001). Evidences of intranasal drug delivery systems formulated using mucoadhesive agents and their benefits in enhancing nose-to-brain drug transport have been reported by various scientists in literature (Alpar et al., 2005; Gavini et al., 2005). It was hypothesized that
Microemulsion based alternative drug delivery systems will result in rapid nose-to-brain transport of drug and distribution into and within the brain. This can help to maximize the therapeutic index of the drug, reduce side effects, decrease the dose and frequency of dosing, and perhaps even the cost of the therapy. The microemulsion concept was introduced as early as the 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol (Hoar and Schulman, 1943; Schulman et al., 1959) and subsequently coined the term micro emulsion. Microemulsions are of various types. They include o/w, w/o and bicontinuous presence of o/w microemulsion droplets. It is likely to be a feature in microemulsions where the volume fraction of oil is low (Fig 1). In contrast, w/o droplets are likely to form when the volume of water is low. In system where the amount of water and the oil are similar, bicontinuous microemulsion may result.

**Microemulsion structure**

The internal structure of microemulsion may be complex and varied. It is physicochemically conceived that on the lower side of water addition, the amphiphile requirement to augment dispersion is low, and on average, a spherical dispersion of amphiphile-coated water nanodroplets exist in oil continuum Winsor I. The situation is opposite for compositions with a low percentage of oil and a high percentage of water Winsor I. The increasing dispersant concentration ends up with increased droplet dimension together with distortion of the spherical shape; at comparable proportions of water and oil, irregular dispersions of both oil and water may simultaneously exist. This is called the ‘bicontinuous state’ which is considered to be a sponge-like random network (Fig. 2, Winsor III). Winsor IV is single phase with oil, water and surfactant homogeneously mixed. Its demonstration by transmission electron microscopy (TEM) has been reported (Moulik and Paul, 1998).

**Brief overview of the current strategies for nasal delivery of hydrophobic drugs**

Microemulsions have evolved as second generation colloidal carrier systems and are being preferred over emulsions in several cases. Microemulsions are thermodynamically stable, transparent, isotropic, low-viscosity colloidal dispersions consisting of microdomains of oil and/or water stabilized by an interfacial film of alternating surfactant and cosurfactant molecules. They include swollen micellar (oil-in-water, O/W), reverse micellar (water-in-oil, W/O) and bicontinuous structures (Tenjarla, 1999; Lawrence and Rees, 2000). Globule sizes of the microemulsions are less than 150 nm. The various advantages such as spontaneity of formation (zero energy input), optical transparency, long-term physical stability, and self-preserving nature give them an edge over conventional emulsions. The potential of microemulsions for various routes of administration has continuously been explored since last two decades. The utility of the microemulsions in dermal, oral and ocular delivery has been reviewed in literature but there is no collective compilation about the applications of microemulsion in nasal delivery (Table 2) (Date and Nagarsenkar, 2008). The present review would focus on the basic aspects of the microemulsions such as structure, phase diagrams, excipients available for the formulation of nasal microemulsions, formulation considerations pertaining to nasal delivery, evaluation of microemulsion and the investigations reported till date. The main objective of the review is to accelerate drug delivery research to extend applications of microemulsions in nasal delivery which is still a niche area.

**Fig. 1** Types of microemulsions.

(a) Oil-in-water microemulsion  (b) Bicontinuous microemulsion  (c) Water-in-oil microemulsion

**Fig. 2** Different phase-forming situations for water-ampiphile-oil mixtures.
Advantages of microemulsion as nasal drug delivery

Ease of manufacturing and scale-up are some of the most important advantages that make microemulsion unique when compared to another drug delivery system like solid dispersion, liposome’s, and nanoparticles. These require very simple and economical manufacturing facility like a magnetic stirrer, sonicator, and volumetric liquid filling equipment for large scale manufacturing. This is of interest to the pharmaceutical industry (Shaji and Joshi, 2005; Bhanushali and Bajaj, 2007; Lianil, 2002).

• Microemulsion has the potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.
• When the mucusadhesive polymer is incorporated in the composition of micro emulsion, it prolongs release of medication.
• Poor water soluble drugs show poor dissolution and bioavailability. Micro emulsion is a novel approach to improve water solubility and ultimate bioavailability of lipophilic drugs. The ability of micro emulsion to present the drug in globule sizes between 1-100 nm subsequently increase specific surface area, therefore resulting in more efficient drug transport from the nasal cavity to the brain leading to improvement in bioavailability.
• Microemulsions provide good sprayability in nasal delivery.
• It provides dose uniformity and formulation physical stability.
• Avoidance of first pass metabolism in liver by some enzymes.
• Ease of administration and better patient compliance.

Formulation considerations and potential ingredients

In general, the phenomenon of microemulsification is mainly governed by the factors such as (1) nature and concentration of the oil, surfactant, co surfactant and aqueous phase, (2) oil/surfactant and surfactant/co surfactant ratio, (3) temperature and pH of the environment and (4) physiochemical properties of the drug such as Hydrophilicity/Lipophilicity, pKa and polarity. Hence, these factors should be given due consideration while formulation of the microemulsions. Formulation considerations with respect to the components of the microemulsions are discussed below (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Potential ingredients of microemulsion.</td>
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<tr>
<td><strong>Ingredient</strong></td>
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<tr>
<td>Surfactants</td>
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<tr>
<td>Co-surfactant/co-solvent</td>
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<td>Oils</td>
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<th>TABLE 2</th>
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<td>Overview of nasal microemulsion.</td>
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<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>Diazepam</td>
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<tr>
<td>Eucalyptus oil</td>
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<tr>
<td>Zolmitriptan</td>
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<tr>
<td>Sumatriptan succinate</td>
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<tr>
<td>Progesterone and Indomethacine</td>
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<td>Clonazepam (CZ)</td>
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Selection of surfactant

Non ionic surfactants, tweens with high HLB values are used in the formulation of micro emulsion. The minimum amount of surfactant in microemulsion is 10% of the total micro emulsion weight. Such large surfactant levels are essential because of the large increase in interface area between the aqueous and oil phase. Hydrophobic surfactant will be suitable for the formulation of w/o microemulsion, and hydrophilic surfactant will form o/w micro emulsion. There are many examples in which hydrophilic surfactant will form w/o micro emulsion in the presence of cosolvent. Many surfactants are used such as ethoxilated and hydrogenated castor oil, i.e. Cremophore EL and Cremophore RH 40, sulfate surfactant i.e. sodium dodecyl benzene, sodium lauryl sulphate, dialkyl sulfo succinates etc. Amphoterics surfactant such as lecithin, quaternary ammonium alkyl salts. Cetyltrimethyl ammonium bromide (CTAB) and dodecylidimethyl ammonium bromide (DDAB) are also excellent surfactant in the formulation of microemulsions (Jha et al., 2008).

Selection of oils

Long chain triglycerides and medium chain triglyceride oils with different degrees of saturation have been used in the design of microemulsion. Other suitable oil phases are digestible or non digestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil, sesame oil, cotton seed oil, sunflower oil, animal fats and short chain triglycerides such as triacetin, MCT (Miglyol 812). Very common oils like iso propyl myristate, jojoba oil or methyl or ethyl oleates are also used.

Selection of cosurfactants

Cosurfactants are incorporated into the interface to keep the film flexible, fluid and tightly packed. They help the surfactant reduce the interfacial tension to very low values to achieve thermodynamic stability. Cosurfactants like ethanol, propanol or butanol are used and polyethylene glycols are commonly used.

Selection of co-solvent

Organic solvents suitable for oral administration include ethanol, propylene glycol and polyethylene glycol, which may help to dissolve large amount of hydrophilic surfactant or drug in liquid base. The addition of an aqueous solvent such as triacetin acts as a cosolvent. Triacetin is suitable because it is miscible in oil/lipid phases and it can be used to solubilize to hydrophobic drugs (Zhang et al., 2004; Tiwari and Bajaj, 2007; Shelke and Devranjan, 2007).

Selection of mucoadhesive polymer

Because mucociliary clearance in the nasal cavity lowers retention time resulting in lower bioavailability, in turn to increase the retention time mucoadhesive polymers were added in microemulsion, e.g. hydroxypropylmethyl cellulose, sodium carboxy methyl cellulose, carbopol 974P, carbopol 971P, carbopol 980 P, polycarboxphil, sodium alginate, xanthum gum, and pluronics PF 127/PF 68.

Phase diagram preparation and microemulsion formulation

Surfactant was blended with co-surfactant in fixed weight ratios (1:1, 2:1, 3:1). Aliquots of each surfactant and cosurfactant mixture (Smix) were then mixed with oil at room temperature (25 °C). For each phase diagram, the ratio of oil to the Smix was varied at 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9,(w/w). Water was added drop wise to each oil. Mix mixture under vigorous stirring. After equilibrium the samples were visually checked and determined to clear microemulsion or emulsion or gels.

Pseudo ternary phase diagram

The pseudo ternary phase diagram was constructed by plotting the amounts of oil phase, water phase and surfactant: the cosurfactant phase used in the experiment (Fig.3). Once micro emulsion region was identified the microemulsion formulation at desired component ratios was prepared with or without drug. The preparation of drug loaded microemulsion was performed by dissolving drug powder into the oil, water phase depending upon solubility, adding required quantity of surfactant- cosurfactant mixture, stirring to form a clear and transparent liquid. The resulting microemulsion were tightly sealed and stored at ambient temperature, and their physical stability was measured by observing periodically the occurrence of phase separation.

Characterization of microemulsion

Clarity: Clarity was observed visually, because microemulsion should be clear and transparent

Dilutability: The microemulsions formed were diluted in 1:10, and 1:100, ratios with double distilled water to check if the system shows any signs of separation. This test is used to check the solubilization of drug and structure of microemulsion whether it is affected upon dilution (Benita, 2006).

Particle size: Particle size analysis is mainly carried out by photon correlation spectroscopy with a Beckman N5 submicron particle size counter which can measure the size range from 5nm to approximately 3 μm. For size analysis approximately 0.1 ml Microemulsion is added to...
10 ml double distilled water in order to obtain the optimum scattering intensity. Another instrument is dynamic light scattering method employing a zeta potential / particle size (Vyas et al., 2004). The particle size of microemulsion should be less than 150 nm. Particles in nanosize loaded with drugs show drug release at right rate and dose at specific sites in the brain for a certain time to realize the accurate nasal delivery, which enhances the therapeutic effect, reduces the toxicity and side effect, decreases the dose and frequency of dosing, and perhaps even the cost of the therapy (Sharma et al. 2007). Nanodroplets are extremely stable will not separate into different phases. The particle size is below 0.22 µm, they can be sterilized by filtration (Vyas and Khar, 2002). Nanoscopic size may have impact on biodistribution of enzymes and peptides (Jain, 2006).

**Centrifugation:** The microemulsion system is centrifuged at 3000 rpm for 15 minutes to determine whether the system shows signs of creaming or phase separation. The system was observed microscopically for appearance.

**Freeze-thaw cycling:** The selected microemulsion, placed in vials was stored at temperature of 4 °c and at 45 °c for 24 hours (single cycle). Five cycles were carried out for the selected microemulsion and the system was observed for any stability.

**pH:** The pH of microemulsion for nasal delivery should be 4.5 to 6.5. Because lysozyme is found in nasal secretion which is responsible for destroying certain bacteria in acidic pH under alkaline condition lysozyme is inactivated and the nasal tissue susceptible to microbial infection therefore advisable to keep pH 4.5 to 6.5.

**Zeta potential:** It should be negative or neutral. Which indicate that droplets of micro emulsion having no charge, that is system is stable. It is determined by using Zetasizer. Zeta potential is essentially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation. To retain the stability of microemulsions it should be zero or neutral.

**Viscosity:** Low viscosity is required to make them good in appearance and easy to handle and packed. Also provide good spray ability, so suitable for nasal delivery.

**Mucoadhesive study:** Mucoadhesion studies were carried out to ensure the adhesion of formulation to the mucosa for a prolonged period of time at the site of absorption. Stronger the bioadhesive force more is the mucosal residence time and so increased the bioavailability of the drug because the nanoparticles adequately adhere on nasal mucosa. The ratio of the adhered nanoparticles is expressed as percent mucoadhesion. But if the mucoadhesion is too strong the formulation can damage to the mucosal membrane. The mucoadhesion study is performed by using two methods i.e. 1) Modified balance method 2) falling liquid film method.

**Stability:** If the formulations showing good stability there is no remarkable change in particle size, drug content, mucoadhesive strength and *in vitro* drug release profile, then formulation showing good stability. Formulations were evaluated at periodical intervals of one month for all parameters. If there is no any major difference in all parameters then the formulations are in acceptable limits. Stability study is performing according to ICH guidelines. Because of thermodynamic stability, they are easy to prepare and require no significant energy contribution during preparation. In the treatment of chronic diseases oil and water based components could be introduce separately into the body in form of stable microemulsion. The formation of microemulsion is reversible. They may become unstable at low or high temperature, but when the temperature returns to the stability range microemulsion reformed; their indefinite stability ensures a long shelf-life.

**Histological study:** It is necessary to examine histological changes in nasal mucosa caused by formulations, if it is to be considering for practical use. Histological studies shows control mucosa (phosphate buffer treated nasal mucosa) stained with hematoxylin-eosin and the effect of formulation on sheep nasal mucosa is observed with help of photomicrographs. Mucosal structure is seen when treated with formulation as compared to the control.

**Delivery of anti-migraine drug**

Migraine headaches appear to be caused by complex interplay of neurologic and vascular changes and show waves of neurologic changes in brain. Essential oils like eucalyptus oil and peppermint oil have been used for aromatherapy for the treatment of migraine. The major active ingredient of eucalyptus oil is cineole (eucalyptol) that has soothing, stimulant and antidepressant effect. Microemulsions have a much greater solubilizing capacity for non-polar organic compounds than aqueous micellar solutions and nasal Eucalyptus oil microemulsion was first reported by (Tiwari and Bajaj, 2007) for intranasal delivery. Eucalyptus oil microemulsions were prepared by combining hydrophilic and lipophilic surfactants namely Tween80, Span80 and Cosurfactant PEG400. Glycerin was added in the formulations as it acts as humectant for nasal formulations. The intranasal spray of eucalyptus oil is a cost effective formulation as the excipients used are easily available. It is an efficient formulation, which provides rapid onset of action.

Another investigation by Vyas and colleagues (Vyas et al., 2006) to prepare microemulsions containing sumatriptan (ST) and sumatriptan succinate (SS) to accomplish rapid delivery of drug to the brain in acute attacks of migraine and perform comparative in vivo evaluation in rats. Sumatriptan microemulsions (SME)/sumatriptan succinate microemulsions (SSME) were prepared using titration method and characterized for drug content, globule size and size distribution, and zeta potential. Biodistribution of SME, SSME, sumatriptan succinate solution (SSS), and marketed product (SMP) in the brain and blood of Swiss albino rats following intranasal and intravenous (IV) administrations were examined using optimized technetium labeled (99mTc-labeled) ST formulations. Higher DTE and DTP for mucoadhesive microemulsions indicated more effective
targeting following intranasal administration and best brain targeting of ST from mucoadhesive microemulsions. Rat brain scintigraphy endorsed higher uptake of ST into the brain. Studies conclusively demonstrated rapid and larger extent of transport of micro emulsion of ST compared with microemulsion of SS, SMP, and SSS into the rat brain. Hence, intranasal delivery of ST microemulsion in this investigation can play a promising role in the treatment of acute attacks of migraine. Sumatriptan microemulsion and sumatriptan succinate microemulsion were prepared using medium chain triglyceride (MCT) as an oil (20% w/w), caprylocaproyl macrogol glycerides as surfactant (S, 27.50% w/w). Mixture (1:1 w/w) of purified diethylene glycol monoethyl ether and fatty acid ester of polyglycerol was used as cosurfactant (Cos, 12.50% w/w) and distilled water (40% w/w) as aqueous phase. Mucoadhesive microemulsion were prepared by addition of polycarbophil (0.5% w/w). The studies demonstrated rapid and larger extent of selective ST nose-to-brain transport compared with SS and SMP in rats. Enhanced rate and extent of transport of ST following intranasal administration of SMME may help in decreasing the dose and frequency of dosing and possibly maximize the therapeutic index. However, clinical benefits to the risk ratio of the formulation developed in this investigation will decide its appropriateness in the clinical practice.

Delivery of antiepileptic drugs

Clonazepam microemulsion (CME) was firstly reported by Vyas et al. (2005) for rapid drug delivery to the brain to treat acute status epileptic patients and to characterize and evaluate the performance of CME in vitro and in vivo in rats. Clonazepam is preferred over other benzodiazepines due to its longer duration of action (24 h). Clonazepam, the drug of choice in suppression of myoclonic seizures, Presently, Clonazepam is available in tablet and injectable dosage forms these formulations release clonazepam into the peripheral circulation resulting in limited drug uptake across the blood–brain-barrier and in drug distribution to non targeted sites (Misra et al., 2003). Intranasal drug delivery also offers the advantages that drugs can be administered simply, cost effectively and conveniently (Liu et al., 2001). Hence, the study deals with the preparation of CME/CMME, biodistribution, and elucidation of transnasal transport mechanism of the drug to justify its role in the treatment of acute status epileptics. CME was prepared (5 mg/mL clonazepam) using medium chain triglyceride as oil (10% w/w), polyoxyethylene-35-ricinoleate as a surfactant (S, 26.67% w/w), polysorbate 80 as a cosurfactant (50% w/w) as an anhydrous continuous phase (Table 3). CME was prepared by addition of polycarbophil (0.50% w/w). (CME), and (CMME) were radio labeled using 99mTc by direct labeling method. The optimized radiolabeled formulations were assessed for in vitro stability in normal saline solution and in rat plasma.

<table>
<thead>
<tr>
<th>Formulation and Route of Administration</th>
<th>Brain Targeting Efficiency (DTE (%))</th>
<th>Direct Nose to Brain Transport (DTP (%))</th>
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<tbody>
<tr>
<td>Intranasal (CMME)</td>
<td>229 ± 4</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>Intranasal (CME)</td>
<td>131 ± 3</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Intranasal (CS)</td>
<td>124 ± 1.5</td>
<td>23 ± 1.5</td>
</tr>
</tbody>
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Mean ± SEM.

Another antiepileptic drug is diazepam (DZ). An ethyl laurate-based micro emulsion system with Tween 80 as surfactant, propylene glycol and ethanol as cosolvents was developed for intranasal delivery of diazepam. For nasal delivery of DZ, two challenges exist in formulation development. One is the requirement of DZ solubilization. The aqueous solubility of DZ is ≥ 50 µg/ml. Since the therapeutic dose of DZ for the treatment of status epilepticus is 5–10 mg and the effective nasal delivery volume is ≤ 300 µl (150 µl/nostril), the target concentration of DZ in nasal formulation is 17–34 µg/ml. After nasal administration, this cosolvent produced a rapid in vivo absorption (tmax=4 min) and a bioavailability of 59%, compared with IV. The addition of 1% sodium glycolcholate further increased the bioavailability to 77% with a tmax of 2 min.

Conclusions

Microemulsions have proved to be useful formulations on commercial scale for nasal delivery of hydrophobic 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 greater solubilizing capacity for non-polar organic drugs than 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


