International Journal for Pharmaceutical Research Scholars (IJPRS)

V-5, I-2, 2016 ISSN No: 2277 - 7873

REVIEW ARTICLE

Mucoadhesive Microemulsion as a Nose-To-Brain (NTB) Transmucosal Drug Carrier

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Manuscript No: IJPRS/V5/I2/00101, Received On: 24/06/2016, Accepted On: 02/07/2016

ABSTRACT

Nose-to-brain (NTB) delivery system is an interesting route to deliver drug substance directly to the brain via the nasal cavity. The unique anatomy of the nasal cavity region may let drug substance to bypass blood-brain-barrier (BBB) and enter the cerebrospinal fluid (CSF). Microemulsion (ME) is an isotropic mixture of oil, water, and surfactant/co-surfactant mixture which has been studied as a drug delivery system for transdermal and transmucosal preparation. Delivering drug via this route has various advantages, including bioavailability improvement and first-pass effect metabolism avoidance. Addition a mucoadhesive agent to a microemulsion-based formulation (Mucoadhesive Microemulsion/MME) has been studied to prolong the retaining time of transmucosal preparation, thus, increase its bioavailability. Drugs for Central Nervous System (CNS) disorder are the drug candidate studied for this delivery pathway. Characterization of prepared microemulsion including interaction study with Fourier-Transform Infrared (FTIR) spectroscopy, conductivity measurement, transmittance percentage measurement, determination of globule size, zeta potential measurement, polarizing microscopy, Transmission Electron Microscopy (TEM), refractive index, viscosity, centrifugation, pH measurement. Nasal ciliotoxicity, mucoadhesive strength and in-situ gel forming capacity also should be determined to confirm its toxicity to nasal cilia and mucous membrane, ability to retain in mucosal membrane and gel forming temperature. Drug release from the MME can be studied by In-Vitro or Ex-Vivo modeling using a vertical diffusion apparatus. In vivo drug release and overall pharmacokinetics study can be performed with animal modeling using rats or rabbit. The radiolabeled intranasally administrated drug can be used to study its brain uptake and overall tissue distribution.

KEYWORDS

Nose to Brain Delivery, Mucoadhesive Microemulsion, Intranasal Route, CNS Disorder

INTRODUCTION

Drug administration via intranasal (IN) route offers various interesting options for topical and systemic delivery. IN route is a non-invasive pathway which offers a quick onset and first-pass effect metabolism avoidance. In addition, gastrointestinal degradation, lung toxicity, and pain during application are absent during IN application.

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It is also easy and ready use by patients or by physicians in an emergency situation. The olfactory and respiratory region of the nasal cavity is a highly vascularized area which provides a good absorption area for topically administrated drug. The fact that olfactory region is located next to cerebrospinal fluid and direct nervous interface to the brain gives an interesting possibility of nose-to-brain (NTB) delivery system[1]. As well as the other routes, IN administration also has its own limitation and

challenge in delivering drug substance. Problems such as poor physicochemical properties of the drug, low permeability of the nasal membrane, nasal enzymatic degradation, and mucociliary clearance are the major problem. The challenges faced during the development stage of an intranasal delivery system are about how to improve the physicochemical characteristic of the drug candidate and overall formulation. Beside the aforementioned challenge, increasing the drug permeability through the nasal mucous membrane, modifying nasal mucous membrane, increasing drug residence time, reduce or protect the drug substance from degradation caused by enzymatic activity as well as inhibit the nasal enzyme and overcome the rapid mucociliary clearance is also things to take into consideration[2].

IN route is an attractive alternative in delivering drug substance directly to central nervous system (CNS). This route offers greater bioavailability because it avoids hepatic metabolism. Drug substance that diffuses via the olfactory epithelial pathway can right end up in the cerebrospinal fluid. Moreover, the olfactory nerve pathway allows direct transport via intracellular space. By this means, administrating drug substance via the intranasal route may have an enhanced bioavailability at the target site (brain), thus, enhance its efficacy[3].

Microemulsion (ME) and Mucoadhesive Microemulsion (MME) for Intranasal Administration

The term "microemulsion" should not be confused with conventional emulsion because the characteristic of both systems is quite different[4]. Microemulsion (ME) is an isotropic mixture and thermodynamically stable system which its formation is a spontaneous process while emulsion is a thermodynamically unstable system, non-isotropic and requires energy during formation. But, like emulsion, microemulsion consists of the oil phase, aqueous phase, and surfactant to stabilize the system. In most cases, the addition of co-surfactant is important to lower the interfacial tension between the two phases. ME droplet size is less than 200 nm. The usage of ME as drug carrier has been studied extensively and lead to the various development of transdermal, parenteral and oral delivery[5,6].

Nasal formulation with microemulsion (ME) base offers various advantages. Because of its ability to dissolve poorly water soluble drugs, most active substances can be incorporated in it. Since it has solution-like properties, (it is a free flowing preparation), it can be introduced to nasal cavity via spray bottle and offers dose uniformity[6]. Other characteristics that make microemulsion based preparation suitable for intranasal administration are the ease of preparation, transparent and elegant in appearance, enhanced penetration through biological membranes, thermodynamic stability, high drug loading capacity, high bioavailability and less inter- and intra-individual variability in drug pharmacokinetics[7]. The ME-based intranasal formulation can give more superior advantages than another common preparation. Botner et al. (2011) claim that midazolam can be dissolved in an alcohol-free microemulsion which not necessitate an acidic pH value, thus decrease epithelial irritation potential while still attaining the desired pharmacological effect. The high loading capacity of the microemulsion system can reduce the application volume of midazolam and diazepam ME preparation[8].

The mucoadhesive agent added into the formulation help to increase retention time in the nasal cavity[6,9]. Incorporating thermosensitive polymer like Pluronic® F-127 or Pluronic® F 68 (in combination with mucoadhesive agent such as sodium alginate, chitosan, Carbopol® 934, Sodium CMC and hydroxypropyl methylcellulose) to form an in-situ gel formulation can further increase the retention time and may provide a prolonged release of the drug from the matrix[7,9]. As reported by Pathak R, et.al. (2014), an in-vivo pharmacokinetic study conducted on nimodipine in-situ gelling nasal ME showed a higher brain and plasma concentration of nimodipine found after administration compared to the nimodipine suspension or microemulsion in rats[7]. The mucoadhesive agent may also act as drug release retardant. Pathak et al. (2004), Patel et al. (2015)

and Samia et al. (2012) reported that drug release (in vitro) in mucoadhesive microemulsion (MME) was prolonged compared to the microemulsion without mucoadhesive agent[7,9,10].

Table 1: Drug Candidate for Nose-To-Brain Delivery System

Drug	Indication	Ref
Remoxipride	Antipsychotic	3
Curcumin	Anti-inflammatory, antioxidant, anticancer	6,11
Nimodipine	Cerebrovascular spasm, senile dementia	7
Quetiapine Fumarate	Antipsychotic	9
Carbamazepine	Antiepileptic	10,12,13
Ziprasidone	Antipsychotic	14
Sumatriptan	Antimigraine	15
Olanzapine	Antischizophrenic	16
Sertraline Hydrochloride	Antidepressant	17
Cabergoline	Hyperprolactinemia, Anti-Parkinson	18
Clonazepam	Antiepileptic	19
Ibuprofen	Protective Agent in Parkinson Disease	20
Paliperidone	Antischizophrenic	21
Mirtazapine	Antidepressant	22
Midazolam	Seizure	(8)
Diazepam	Seizure, Insomnia	8,23
Lorazepam	Insomnia	23
Alprazolam	Insomnia	23
Vinpocetine	Antiischemic	24
Ropinirole	Anti-Parkinson	25
Clobazam	Antiepileptic	26
Risperidone	Antipsychotic	27,28

Nose-To-Brain (NTB) Delivery and the Drug Candidate

In route offers a lot of interesting possibilities. Aside from local disorder treatment, intranasal administration is a simple, economic, convenient and non-invasive route for rapid drug administration into the systemic circulation such as for peptide, vaccine, analgesic, anti-angina, etc.[2]. As for Nose-To-Brain delivery system, a lot of studies on the drugs for CNS disorder treatment (like-schizophrenia, migraine, epilepsy, and depression) have been conducted.

Brain and nasal cavity are connected to each other via olfactory/trigeminal route via peripheral circulation. Administrating drug via this route can bypass the Blood-Brain-Barrier (BBB) and reduce the number of the drug distributed to its non-target organ, hence giving the advantages of no dose reduction, no systemic dilution and no first-pass hepatic metabolism[14]. Vyas et al. (2006) reported that a 2.5- to 3.0-fold higher brain/blood drug concentration ratio was showed in a study involving intranasal administration of mucoadhesive microemulsion of sumatriptan compared to IV administration of drug microemulsion[15]. Although oral dosage form like tablet is also available for most drug, delivering anti-seizure drug directly to the brain like diazepam can be benefit since oral route is not accessible during seizure episode and fast acting nasal delivery route may be an alternative since it is easily administered by the surrounding people or caregivers and could improve the management of out-of-hospital seizures as well as the patient recovery[8]. Some of the drug candidates studied for Nose-To-Brain delivery system listed in Table 1.

Formulation

Construction of Phase Diagram

Microemulsion formation is a spontaneous process which will happen only if the oil-water-surfactant and co-surfactant mix (Smix) is in the correct ratio. Construction of phase diagram (usually pseudo-ternary phase diagram) is an important step to determine the correct proportion of each phase. It is important to

carefully determine each area (microemulsion, liquid crystal, macroemulsion, bicontinuous structure) and metastable structure should not be included. Phase titration method is one of the most used methods with fixed oil and Smix ratio. The aqueous phase is gradually titrated into Smix and oil mixture. Each corner represents 100% portion of each phase[8,29].

A microemulsion phase is clear, single-phase and isotropic mixture. An opaque system showing birefringence with oily streaks, fan-shaped texture, when viewed by cross-polarized light microscopy, will be classified as lamellar crystal system while the system consisting of two phase when examined under a phase contrast microscope and shows birefringence under a cross-polarizer will be classified as a macroemulsion[14].

Excipient

Oil Phase

Selection of oil phases is an important step since the oil phase should be able to solubilize the active substance[29]. The screening usually involves a preliminary solubility study (in both oil and Smix phase. If the drug is more soluble in oil phase than in the Smix phase, more reservoir effect and more partitioning of the drug in oil phase will be experienced and sustained drug release win be achieved like what had been reported by Mandal et al. (2006) with Curcumin loaded MME[6]. Several oil phase that have been screened for nose to brain delivery system are glyceryl monooleate (Peceol)[7–9], castor oil[9, 14], lemon oil[9], oleic acid[6, 9, 10, 14, 16, 21], linoleic acid[9], isopropyl myristate[6, 9, 14, 16, 17, 20, 21], glyceryl caprylate/caprate (Capmul MCM, MCM EP, MCM-L8)[6,7,16–18,20–22], ethyl laurate[17], glyceryl mono linoleate (Maisine)[7], propylene glycol dicaprylate/dicaprate (Labrafac CC, PG, Lipophile) (6,12,16,20–22), Oleoyl macrogol-6 glycerides (Labrafil M 1944CS, 2125)[6, 7, 12, 16, 18, 21, 22], Propylglyceryl oleate (Plurol oleique CC)[16,21,22], propylene glycol monolaurate (Lauroglycol 90)[16,21], caprylocaproyl macrogol glyceride[15], diethylene glycol monoethyl ether[15], isopropyl palmitate[8], glyceryl monostearate[24]. Some of these oil phases are also used as a permeation enhancer.

Surfactant and Co-Surfactant

Surfactant and co-surfactant mixture (Smix) play a significant role in determining the microemulsion characteristic. High proportions of surfactant and co-surfactant mixture in formulation decrease the bending stress of interface and give the interfacial film sufficient flexibility to take up different curvature required to form microemulsion over an extensive range of composition. This may be due to the manifestation of low molecular weight surfactant being able to influence the formation of microemulsion by both interfacial and bulk effects. The interface area relates with surfactant layer via hydrophobic chain and terminal hydroxyl group which also affect their arrangement. This, in turn, can affect the curvature of the interface and interfacial energy. Co-surfactant with low molecular weight enables them to distribute between the two phases thus altering their relative hydrophilicity-lipophilicity properties. Most single-chain surfactant does not satisfactorily decrease the interfacial tension between the aqueous and oil phase to form microemulsion and the addition of co-surfactant, like short-to-medium chain alcohols, is necessary for this circumstance. This co-surfactant addition can also guarantee the flexibility of interfacial film is enough to deform when needed around each droplet as their intercalation between the main surfactant molecules decreases both the polar head group interaction[9, 12]. Some of screened surfactants for nose to brain delivery are Accenon CC[6,20], polyoxyl 40 hydrogenated castor oil (Cremophor RH 40, EL) [6,12,14,16,20,21], Tween-20[9], Tween-60[6,9,20], Tween-80[6, 7, 9, 14, 16, 17, 19–22], Labrasol[7, 8, 10, 16, 18, 21, 22], Acrysol K40[9], Solutol H515[9], Poloxamer 124[9], polyoxyethylene 35-ricinoleate[19], Span 20[14]. Some of screened co-surfactants are PEG 200[9], PEG 400[6,7,9,20,22], PEG 600[6,20], propylene glycol[6,9,12,14,17,19,21], glycerol [6,20], isobutyl alcohol[6, 9, 20], isopropyl alcohol[6,9,20] and diethylene glycol monoethyl ether (Transcutol P) [6,7,9,12,16–18,20–22]

Mucoadhesive Agent and In-Situ Gel Forming Agent

Mucoadhesive agent and sometimes in combination with in-situ gel forming agent are added into the formulation to attain better residence time, reduced mucociliary clearance and better bioavailability than the usual microemulsion system[7]. Mucoadhesive polymers like cellulose, polyacrylate, starch and chitosan have confirmed as an effective agent to increase nasal absorption of hydrophilic macromolecules. These polymers can increase the drug residence time in the nasal cavity or enhance intranasal absorption and some of them can serve both functions. Since most of these polymers are commonly known as a safe pharmaceutical excipient and not absorbed into systemic circulation, the systemic toxicity may not be showed[30]. Some of the screened mucoadhesive agents for ME based preparation are polycarbophil[6,12,15,16,18–21], xanthan gum[10], chitosan[9, 17, 18, 22, 25], carbomer (Carbopol 934 P)[7], sodium alginate[7], sodium CMC[7] and for in situ gel forming agent are poloxamer polymers like Pluronic F127[7,9], Pluronic F68[7] or cellulose derivate like HPMC[25] which are thermosensitive polymer or deacetylated gellan gum (DGG)[11], an ion-sensitive gel-forming agent.

Characterization of Microemulsion

Interaction Study with FTIR

Chemical interaction study between drug substance and excipient should be established by observing any change of IR spectrum from the drug and excipients in the formula. Any changes in their spectrum indicate the presence of chemical interaction[9].

Conductivity Measurement

Conductivity measurement is useful in approximating the structure of microemulsion. Measurement can be performed using calibrated conductivity meter[14].

% Transmittance Measurement

Transmittance measurement is performed by measuring the transmittance of the diluted formulation with UV-Vis Spectrophotometer or Colorimeter at a certain wavelength. The effect of dilution should be checked (like on globule size or phase separation). The continuous phase is used as the diluent and water as blank[9, 16].

Determination of Globule Size

Mean particle size and size distribution (polydispersity index) is measured using a particle size analyzer, dynamic light scattering or Zetasizer. The sample is diluted up to 100x dilution factor and determined by light scattering based on laser diffraction under controlled temperature when using particle size analyzer or by photon correlation spectroscopy when using Zetasizer[6, 8, 9, 16].

Zeta Potential

Zeta potential of microemulsion droplet is determined using Zetasizer or particle size analyzer with zeta potential measurement option after dilution with double distilled water. The dilution is important to acquire the scattering intensity allowing optimal particle detection. The collection of zeta potential data is useful in the assessment of microemulsion physical stability [9, 14, 16].

Polarizing Microscopy

The microemulsion is placed on a glass slide and examined under cross-polarized light microscopy to verify the isotropic nature of the formulation[21].

Transmission Electron Microscopy (TEM)

TEM is used to characterize the microstructure of microemulsion. Diluted sample microemulsion is placed on a carbon-coated copper grid and covered with a drop of 1% phosphotungstic acid. TEM imaged obtained using suitable software[6,21].

Refractive Index

The refractive index can be measured using a refractometer. A drop of the microemulsion is placed on the glass slide and examined[14].

Viscosity

The rheological study can be examined by viscosity determination performed using viscometer. Spindle type, spindle number, and speed should be noted. The measurement should

be done at ambient temperature and when the microemulsion reaches its equilibrium[7,14,21].

Centrifugation

Centrifugation can be used to evaluate the physical stability of prepared microemulsion. The microemulsion is centrifuged for 10 minutes at 5000 rpm. Visual observation is performed after centrifugation to find any creaming or phase separation[31].

pH Measurement

pH measurement is performed using calibrated digital pH meter. The electrode can be directly immersed to the prepared microemulsion or into diluted samples (up to 100x dilution factor)[14, 20].

Mucoadhesive and In Situ Gel Forming Time

An instrument like Brookfield texture analyzer can be used to determine mucoadhesive strength. The instrument is connected to 34-mm probe to which goat nasal mucosa was appended. At the other end, the mucoadhesive microemulsion is prepared. Goat nasal mucosa then exposed to the formulation for about 30 seconds and allowed to detach to obtain load versus time behavior of the formulation[9].

In situ gel forming of a formulation containing thermosensitive polymer can be determined by a tube method used by Khan et al. (2010). Prepared MME (about 2.0 ml) is added into a 10 ml tube with 1.0 cm diameter and keep in a controlled temperature water bath. The tube is taken out every 1 min and inverted. The time required by the MME to form a gel at 37 ± 1°C is determined by flow or no-flow criteria after inverting the tube for over 30 s[25].

Nasal Ciliotoxicity

Potential toxic effect test of the excipient to nasal cilia should be established. A study can be conducted on various animal nasals mucous as the model. Histological study on rat's nasal mucous membrane is conducted after introducing nimodipine in situ mucoadhesive microemulsion by Pathak et al. (2014). The mucous membrane is collected after 24-h post administration and sectioned using microtome. The tissue then stained and observed under a microscope for any alteration of tissue structure or necrosis[7]. Another study is conducted using fresh sheep nasal mucous membrane drug loaded microemulsion. Three membranes with uniform thickness are collected and treated with the formula, PBS as a negative control and isopropyl alcohol as a positive control for 1 hour. After 1 hour, the tissue is rinsed with PBS, treated with formalin and paraffin sectioned using microtome and stained before histological examination under a light microscope[6, 9, 16, 21]. Kumar et al. (2009) use goat nasal mucous membrane in their study[17] while Wang et al use Wistar rats in their study with sodium deoxycholate solution for the negative control[11].

In Vitro and Ex Vivo Permeation Study

In vitro permeation study can be performed using vertical diffusion cell like Franz Diffusion Cell or Keishery-Chein type diffusion cell. A dialysis membrane with a molecular weight from 12.000 to 14.000 kDa can be used as diffusion membrane (for example, cellophane membrane). The membrane should be treated with buffer solution (for receptor compartment) 24 hours prior usage. Phosphate buffer pH 7.4 can be used as the permeation medium. The sample is placed in the donor compartment while the permeation medium is preheated to 37°C and placed in the receptor compartment with constant stirring with magnetic stirrer. The permeation study is carried out for 4 hours and the temperature should be maintained at 37±1°C during the process. Sampling time and aliquot volume should be predetermined as desired (for example 5 ml each 30 minutes). After each sampling, the same amount of media should be compensated. Determination of permeated drug can be performed with spectroscopic method[9,14].

For ex vivo study performed by Patel et al. (2015), fresh superior nasal membrane from sheep (with uniform thickness around 0.2±0.1 mm) is used. After collection, the nasal membrane then equilibrates in PBS pH 7.4 for 15 minutes. The membrane then mounted in Franz diffusion cell. Phosphate buffer pH 5.0 is added in both compartments to stabilize the tissue membrane and stirred for 15 minutes. The buffer

solution is replaced after that. The receptor compartment then filled with fresh PB pH 5.0. Any leakage on the diffusion cell should be avoided prior the test. The next treatment is similar with in vitro study. During the test, the temperature should be maintained at 37±1°C. The same amount of media should be replaced after each sampling. The test is carried out for 12 hours. The amount of the diffused drug is analyzed using a UV-Vis spectrophotometer. Cumulative percentage of the diffused drug then calculated and plotted against the time. The diffusion coefficient is determined using the plot[9].

In Vivo, Brain Uptake, Bio-distribution, and Pharmacokinetic Study

The brain distribution study can be performed by animal modeling. The test animal (for example, Swiss Albino male rats, 4 to 5 months old, 200 to 250 gram in weight) is grouped and administrated with radiolabeled preparation. Technetium-99m (^{99m}TC) is used as radiolabel in several research[15,18,19]. The radiolabeled complex of the drug (100 µCi/50 µL to 150 µCi/50 µL) then administrated in each nostril (10 µl each) with micropipette mounted with LDPE tubing having 0.1-mm internal diameter at the delivery site. Rats can be anesthetized before to ease the administration[15,18]. The same dose (20 µl) is administrated to a different group through the tail vein. The rats are killed humanely for each different time intervals. The blood sample then collected with a cardiac puncture. Brain and other tissue are dissected, washed with normal saline solution and weighed. Radioactivity present in each tissue/organ is measured using shielded well-type gamma scintillation counter. Radiopharmaceutical uptake per gram in each tissue and organ is calculated as a fraction of the given dose using equation 1[18].

$$\frac{\%\ radioactivity}{gm\ of\ tisue} = \frac{counts\ in\ sample\ x\ 100}{weight\ of\ sample\ x\ total\ count\ injected} \quad \ldots\ldots\ldots\ldots\ldots\ (1)$$

Drug brain concentration versus time is made and the pharmacokinetic parameters are calculated. The brain targeting efficiency is evaluated based on the drug targeting efficiency (DTE%) value which represents time average partitioning of the drug between brain and blood's brain drug-direct transport percentage (DTP%) value which represent the percentage of drug transported to the brain through the olfactory and trigeminal neural pathway. DTE% and DTP% are calculated using equation 2,3 and 4[18].

$$DTE\% = \frac{\left[\left(\frac{AUC_{brain}}{AUC_{blood}}\right) in\right]}{\left[\left(\frac{AUC_{brain}}{AUC_{blood}}\right) iv\right]}\ x\ 100 \quad \ldots\ldots\ldots\ (2)$$

$$DTP\% = \frac{B_{in} - B_x}{B_{in}}\ x\ 100 \quad \ldots\ldots\ldots\ldots\ (3)$$

$$B_x = \left(\frac{B_{iv}}{P_{iv}}\right)\ x\ P_{in} \quad \ldots\ldots\ldots\ldots\ (4)$$

B_x Brain AUC fraction contributed by systemic circulation through the blood–brain barrier (BBB) following intranasal administration.

B_{iv} $AUC_{0\rightarrow240}$ brain following intravenous administration.

P_{iv} $AUC_{0\rightarrow240}$ blood following intravenous administration.

B_{in} $AUC_{0\rightarrow240}$ brain following intranasal administration.

P_{in} $AUC_{0\rightarrow240}$ blood following intranasal administration.

AUC Area under the curve.

Stevens et al. (2011) and Patel et al. (2015) use Male Sprague–Dawley (SD) rats in their pharmacokinetic study. The femoral artery is cannulated with polyethylene tube under anesthesia and blood is collected from the cannula. The prepared formula is instilled into each nostril. Blood samples are collected at predetermined times after intranasal administration. After each sampling, sample (heparinized blood sample or blood sample in EDTA coated vial) then centrifuged. The drug content in the plasma is determined with a suitable instrument. The pharmacokinetic parameter is calculated based on the collected data[3, 9]. To study drug concentration in brain extracellular fluid, a micro-dialysate tubing can be implanted and the microdialysate sample can

be collected in a predetermined time interval as shown by Stevens et al. (2011)[3].

A healthy, 2,0 to 3,5 kg weight, white New Zealand rabbit used by Botner et al. (2011) for pharmacokinetic study. Main ear artery is cannulated and approximately 100 µl of the formulation is administered via intranasal route (50 µl in each nostril). Blood sample then collected in a heparinized tube, centrifuged and analyzed[8]. Thakkar et al. (2013) use Wistar rats for their study[22].

CONCLUSION

Delivering drug moieties via the intranasal route to target the brain is a promising alternative to treat various CNS disorder. Microemulsion based preparation with mucoadhesive agent addition can be administrated intranasally and exhibits greater advantages than another route to deliver the drug directly to the brain. A preliminary study such as the construction of phase diagram and excipient selection should be performed and characterization of the preparation is made to differentiate microemulsion system from another biphasic system that may be formed. In vitro and ex vivo study followed by an in vivo and pharmacokinetic study can be established as a comprehensive study to confirm in vitro-in vivo correlation after intranasal administration.

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