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A Review on Microemulsion Drug Delivery System for Nasal Application

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Abstract

Microemulsions are excellent candidates as potential drug delivery system because of their improved drug solubilization, long shelf life and ease of preparation and administration. These versatile systems are thermodynamically stable, colloidal dispersion of water and oil stabilized by surfactant and cosurfactant. It provides protection against oxidation, enzymatic hydrolysis and improves the solubilization of lipophilic drugs and hence enhances their bioavailability. In addition to oral and intravenous delivery, they are amenable for sustained and targeted delivery through ophthalmic, dental, pulmonary, vaginal and topical routes. In this present review article, we discuss about the various advantages of microemulsions in pharmaceuticals, along with its preparation, characterization and research work carried out on microemulsions.

Keywords: Surfactant, Lipophilic drugs, Microemulsions, Thermodynamically stable, Bioavailability.

1. INTRODUCTION OF NASAL DELIVERY :

Intranasal administration therapy also called "Nasya karma" was mostly used form of treatment in the past and also accepted in Ayurvedic system of Indian medicines. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to the other conventional drug delivery route[2-3]. Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects[4-5]. The nasal cavity is mainly used for treatment of local diseases of the upper respiratory tract such as nasal congestion, nasal infections and nasal allergic diseases e.g. allergic rhinitis. However, in the last decades the nasal cavity has also been exploited for systemic delivery of small molecular weight drugs, especially where a rapid onset of action is required. Examples of such marketed nasal product are drugs for treatment of Rhinosinusitis e.g. Azelastine (Asteline), Beclomethasone (Beconase) and budesonide (Rhinocort), treatment of pain management e.g. fentanyl (Instany), for smoking cessation (Nicotrol NS) and for treatment of prostrate cancer e.g. Buserelin (Superfact), and has resulted in a variety of different medications including corticoids, antihistamines, anticholinergic and vasoconstrictors. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug delivery. Only a few nasal delivery systems used in experimental studies are currently on the market to deliver therapeutics into the nasal cavities, i.e. nasal drops as multiple or single-dose formulation, aqueous nasal sprays, a nasal gel pump, pressurized MDIs and dry powder inhalers. Intranasal delivery is currently being employed in treatments for include cancer therapy, epilepsy, antiemetic's, rheumatoid arthritis and insulin dependent diabetes[6]. An examination of the causes of the failure led to the conclusion that the short residence time of the formulation within the nasal cavity coupled with the low permeability of the latter did play significant roles. Even though a number of challenges are still to be overcome, the potential of nasal drug delivery; including the ability to target drugs across the blood-brain barrier(BBB); the systemic delivery of small molecular weight drugs, especially where a rapid onset of action is required; is very high[4]. The nasal drug delivery is a useful delivery method for drugs that are active in low doses and show minimal oral bioavailability. Currently, two classes of nasally delivered therapeutics are in the market. The first one has a low molecular weight and comprises of hydrophobic drugs for the treatment of the nasal mucosa and sinus; including decongestants, topical steroids, antibiotics, antihistamines, vasoconstrictors and other products. The second class encompasses drugs, which have sufficient nasal absorption for displaying systemic effects. Therefore, the nasal delivery is a promising alternative route for the administration of drugs whichundergo a first pass metabolism[7].

1.1.1 *Advantages of Nasal drug delivery system:*[8,9,10,11]

1. Easy accessibility and needle free drug application without the necessity of trained personnel facilitates self-medication, thus improving patient compliances compared to the parenteral routes.
2. Good penetration of, especially lipophilic, low molecular weight drugs through the nasal mucosa.
3. Rapid absorption and fast onset of action due to relatively large absorption surface and highly vascular.
4. Avoidance of the harsh environmental conditions in the gastrointestinal tract (chemical and enzymatic degradation of drugs).
5. Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.
6. Potential for direct delivery of drug to the central nervous system via the olfactory region, thus by passing the blood brain barrier.
7. Direct delivery of vaccine to lymphatic tissue and induction of a secretory immune response at distant mucosal site.

8. *Ease of administration:* Nasal devices, such as metered dose nasal sprays, are simple for the patient to use and might be expected to be more acceptable to the patient to use and might be more acceptable to the patient than the use of pessaries or suppositories for the intravaginal and rectal delivery routes respectively.
9. The nasal route may become a useful alternative to the intestinal route for drug absorption in situations where use of the gastrointestinal route is unfeasible.
10. Offers lower risk of overdose.
11. The nasal epithelium is thin and highly vascularized. This ensures a high degree of absorption and a rapid transport of the absorbed substances into the systemic circulation which accords a rapid onset of therapeutic effect.

1.1.2 Limitation of Nasal drug delivery system:[8,9,10,11]

1. *Mucociliary clearance:*Mucociliary clearance reduces the retention time of drugs within the nasal cavity and thus the opportunity for absorption. For drugs which are rapidly absorbed, mucociliary clearance is likely to be of little consequence, but for those compounds with physicochemical properties dictating slow absorption the effect of mucociliary clearance is likely to be profound.
2. Drug diffusion may be limited by the physical barrier of the mucus layer and the binding of drugs to mucins.
3. Delivery is expected to decreases with increasing molecular weight of drug.
4. Difficult t administered drug in pathological condition such as nasal congestion due to cold or allergic reactions.
5. Some drugs cannot administered throw this route because they cause nasal irritation.
6. There could be mechanical loss of dosages form into the other part of respiratory tract like lungs because of the improper technique of administration.
7. The histological toxicity of different type of penetration enhancer used is not clearly known.

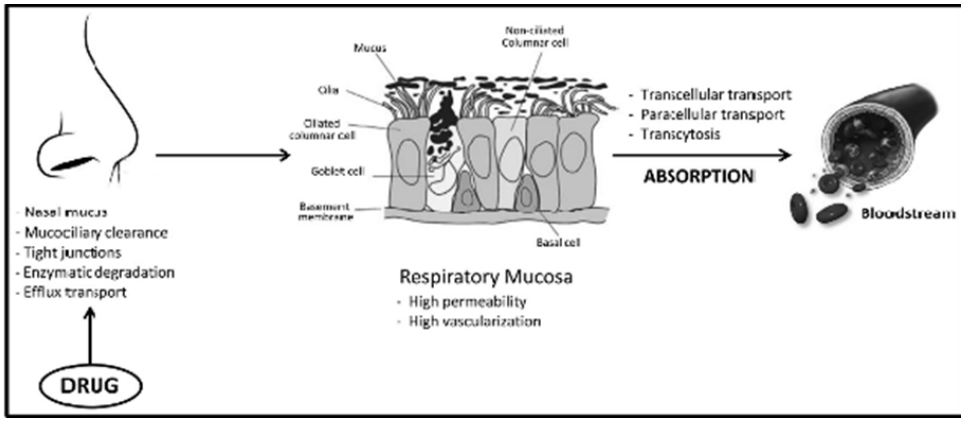

Figure 1.1 Schematic representations of the respiratory mucosa and the possible pathways involved in the transport of drugs from nose to systemic blood stream. Factors that influence systemic absorption of nasal drugs are also represented[5].

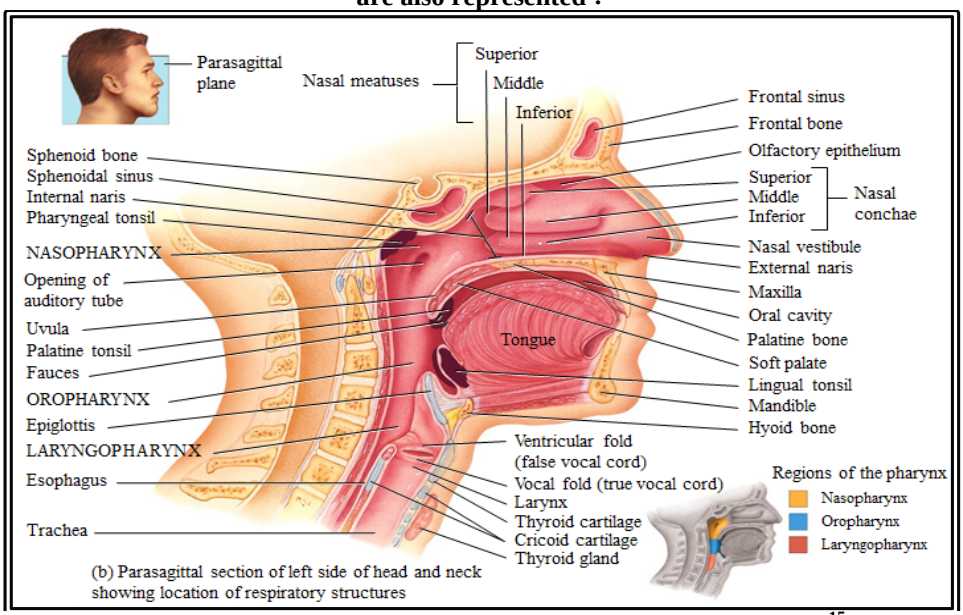

Figure 1.2 : Sagital section of the left side of the head and neck [15]

2. NASAL: Anatomy, Physiology and Histology

2.1. Morphology of the nose:

The main functions of the nose are olfaction, regulation of humidity and temperature of inhaled air, and removal of large particulates including microorganisms from the inhaled air. The nasal septum divides the nasal cavity along the center into two halves open to the facial side and to the rhinopharynx, through the anterior and via the posterior nasal apertures, respectively. Each nasal cavity can be divided into three regions; the nasal vestibule, the olfactory region and the respiratory region[12-13]. The human nasal cavity has a total volume of 15-20ml and only extends approximately 12-14cm in length yet has a large absorptive surface area of 160cm² due to three bony structures called turbinates or conchae (inferior, middle and superior)[14].

2.2. Anatomy:

2.2.1 Vestibule of nose:

Anterior and inferior part of nasal cavity is called the vestibule. It is lined by skin and contains sebaceous glands, hair follicles and the hair called *vibrissae*. Its upper limit on the lateral wall is marked by limen nasal (nasal valve) which is formed by the caudal margin of upper lateral cartilage. Its medial wall is formed by the columella and lower part of the nasal septum up to its mucocutaneous junction[17].

2.2.2 Atrium:

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted with a stratified squamous and transitional epithelium and the posterior area with pseudo stratified columnar cells projecting microvilli. Thin sheet of mucus produced from the seromucus gland and globet cells covers the nasal turbinate and the atrium[18,2].

2.2.3 Respiratory region :

The nasal respiratory epithelium lines approximately 50% of the nasal cavity in rats and 80-90% in humans. It is a pseudo stratified columnar secretory epithelium which warms and humidifies inspired air in addition to removing particulates, micro-organisms, and allergens. The humn respiratory epithelium is comprised of globet cells, ciliated cells, intermediate cells, and basal cells[19]. Serous glands, seromucous glands, and intraepithelial glands are also associated with the nasal respiratory epithelium. The seromucous glands are responsible for producing most nasal secretions while the globet cells also secrete mucus[20]. The primary role of the ciliated cells is to use their motile cilia, immersed in periciliary fluid, to propel mucus towards the nasopharynx where it is either swallowed or expectorated. Basal cells function as progenitors to the other cell types in the nasal respiratory epithelium is innervated by branches of the trigeminal nerve[21]. A portion of trigeminal ganglion cells with sensory endings located in the nasal epithelium also send collaterals directly into the olfactory bulb in addition to the brainstem. The trigeminal motor nucleus, located in the upper pons, contains the nuclei of motor neurons that travel in the small motor root to the muscles of mastication[22].

2.2.4 Olfactory region:[22,23]

The olfactory region comprises 10% of the surface area of the nasal epithelium in man. It consists of a pseudo stratified columnar epithelium located on the most superior aspect of the nasal cavity that is responsible for mediating the sense of smell. Olfactory sensory neurons(OSN) have several unique attributes, they are the only first order neurons possessing cell bodies located in a distal epithelium and the tips of their dendritic processes, which end as enlarged knobs with several non-motile cilia, extend far into the overlying mucus layer that is directly exposed to the external environment. The OSN are bipolar cells possessing odorant responsive receptors in the plasma membrane of the olfactory cilia; easy access of odorants to OSN receptors in the mucus lining the olfactory epithelium is essential to the process of olfaction. Olfactory information is then sent through axons of the mitral and tufted cells to a number of areas including the anterior olfactory nucleus, olfactory tubercle, piriform cortex, and amygdala and entorhinal cortex. Several other types of cells reside in the olfactory epithelium in addition to OSN. Blood vessels, inflammatory cells, and lymphatic vessels which drain into the deep cervical lymph nodes in the neck are also present in the submucosa (lamina propria) of the olfactory region.

2.3 Physiology of nasal mucosa:

2.3.1 Blood flow:[25]

Rich supply of blood and a large surface area make the nasal mucosa an optimal location for drug absorption. Nasal absorption of drugs is influenced by blood flow rate, as it increases the amount of drug that passes through the membrane and hence reaching the general circulation. Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air therefore the drug absorption will depend upon the vasoconstriction and vasidilation of the blood vessels.

2.3.2 Nasal pH:[26]

The normal pH of the nasal secretions in the adult ranges approximately from 5.5 to 6.5, whereas in infants and young children it ranges from 5.0 to 6.7. A nasal pH of 6.5 or below has been believed to be critical for preventing the growth of pathogenic bacteria in the nasal passage. Lysozyme is a substance found in various body tissues and secretions, including nasal secretions, and has the ability of dissolving certain bacteria. The activity of lysozyme is influenced by the hydrogen ion concentration in the nasal secretion with the optimum pH in the slightly acidic region.

2.3.3 Nasal secretion and mucus:[27,28]

Quantity of nasal mucus, comprise both mucus cells, secreting the mucus gels, and serous cells, producing a watery fluid. Seromucus glands in the human nose have been estimated to100,000. Mucus is also released from the globet cells as mucus granules, which swell in the nasal fluids to contribute to the mjucus layer. Mucus secretion is a complex mixture of many substances and consists of about 95% water, 2% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulin's, lysozyme and lactoferrin, and 1% lipids. The production of IgA by

both the adenoid tissue and the nasal mucosa contributes significantly to the immune protection against inhaled bacteria and viruses. This mucus blanket, about 5 cm thick, consists of two layers, a lower sol layer and an upper gel layer. The viscocity of both layers affects ciliary beating and the efficiency of transporting the overlying mucus the mucociliaryclearance(MCC). The nasal mucus performs a number of physiological functions.

- It covers the mucosa, and physically and enzymatically protects it.
- The mucus has water holding capacity.
- It exhibits surface electrical activity.
- It permits efficient heat transfer.
- It acts as adhesive and transports particulate matter towards the nasopharynx.

2.3.4 Mucociliary clearance (MCC) :[29-31]

The function of the mucociliary clearance system is to remove foreign substances and particles from nasal cavity , thus preventing them from reaching the lower airways. The mucociliary clearance system has been described as a "conveyer belt" in which ciliated cells provide the driving force, and mucus performs as a sticky fluidic belt that collects and disposes of foreign particles. The efficiency of the mucociliary clearance system is therefore dependent on the physiological control of the ciliated cells and on the rheological properties of the mucus blanket, other cilia catch up with it and transfer their energy to the mucus as well. While the effective stroke propels the overlying mucus forward, the underlying periciliary fluid only moves forward and backwards during the beat cycle. The mucus blanke in the nose is transported towards the nasopharynx, where it is swallowed. Normal mucociliary transit time in humans has been reported to be 12 to 15 min. Transit times of more than 30 min are considered to be abnormal, and are indicative of impaired mucociliary clearance. The average rate of nasal clearance is about 8 mm/min, ranging from less than 1 to more than 20 mm/min. In a study of 46 healthy subjects, mucociliary transport was found to be independent of sex or age. Radiolabelled nasal sprays exhibit biphasic clearance from their site of deposition. The first phase of clearance lasts about 15-20 min.In which about 50% of the administered dose is cleared from the ciliated respiratory mucosa.

2.3.5. Biophysics of nasal mucus:[32-33]

Mucin is the major component of mucus. This compound, primarily responsible for the viscoelastic properties of the mucus.Mucins are heterogeneous macromolecules composed of approximately 10-30 % weight of peptide core linked to oligosaccharide chains that make up 70-80% of the total weight. Viscoelasticity is the most extensively investigated physiochemical property of mucus. The viscoelasticity depend on the mucin, water and other ions present, with small changes in, e.g., water or pH significantly altering the viscoelasticity. The presence of phohspholipids (in the mucus) confers surface active properties to it. The surface activity can have a powerful impact on either the stability or the permeability of compounds following emulsification in the mucus layer. According to Meyer and Silberberg, non-covalent forces are responsible for maintaining the tertiary structure of mucin. Intercarbohydrate bonds together with contributions from disulfide bonds provide a zipper-like association between mucin chains to interact and entangle.

2.3.6. Nasal enzyme:[34,24]

Internasally administration of drugs avoids gastrointestinal and hepatic first-pass effect. Drugs may be metabolized in lumen of nasal cavity due to the presence of a broad range of metabolic enzymes in nasal tissues. Some examples of enzyme which may play role in enzymatic degradation of drugs are carboxyl esterase, aldehyde dehydrogenases, and epoxide hydrolases, glutathione S-transferases and Cytochrome P450 isoenzymes have been found in nasal epithelial cells. The proteolytic enzymes (amino peptidases and proteases) were also found and they play an important role in degradation of calcitonin, insulin and desmopressin. The pharmacokinetic and pharmacodynamics profile of drugs administered through nasal route may be affected by xenobiotic metabolizing enzymes.

2.3.7. Transporters and efflux systems:[35,36]

The absorption of drugs into systemic circulation and CNS through nasal route is of great interest. Multi drug resistance transporters have been identified which may be involved in the transportation of hydrophobic and amphiphilic drug. The apical area of ciliated epithelial cells and sub mucosal vessels of the human olfactory region contain P-gp is an efflux transporter which plays an important role in avoiding the influx of drugs from nasal membrane.

2.4.1. Pathways for nasal absorption:

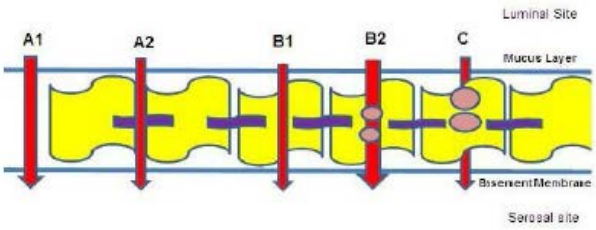

Figure 1.4 : Pathways for nasal absorption-(A1) Intercellular spaces, (A2) Tight junctions, (B1) Passive diffusion, (B2) Active transport, (C) Transcytosis[6]

2.4.2. Transport route of nasal :

2.4.2.1 The paracellular route[23]

The paracellular permeability of the nasal epithelium is approximately the same as that of the intestine, thus small hydrophilic molecules can passively diffuse between adjacent cells. Passive diffusion between the cells is driven by a concentration gradient, with the rate of absorption governed by fick's first law of diffusion.

2.4.2.2 The tanscellular route[37,23]

The transport across the epithelial cells, which can occur by passive diffusion, carrier-mediated transport, and endocytic processes (e.g., tanscytosis). Traditionally, the transcellular route of the nasal mucosa has been simply viewed as primarily crossing the "lipoidal barrier", in which the absorption of a drug is determined by the magnitude of its partition coefficient and its molecular size.

2.4.2.3 Transcellular passive diffusion[38]

For most conventional drug molecules, which tend to be small and lipophilic, absorption occurstranscellularly, by passive diffusion across the cells of the epithelium. Again, movement occurs down a concentration gradient, according to fick's first law of diffusion. The degree of ionization of a drug species is an important property for absorption via passive transcellular diffusion and is dependent on the pKa of the drug and the pH of the environment; the pH of nasal secretions is normally in the region 5.5-6.5.

2.5 Factors affecting the nasal absorption:[39]

Many factors affect the systemic bioavailability of nasally administered drugs. The factors can be attributed to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal passage and the type and characteristic of selected nasal drugs delivery system.

1) Physicochemical Factors

- Charge
- Molecular weight
- Lipophilicity

2) Formulation Factors

- pH
- Osmolarity
- Viscocity
- Concentration
- Volume
- Dosage form

2.5.1 The factors influencing nasal drug absorption:

Table No 1.1 : The factors influencing nasal drug absorption

Physicochemical Properties of drug	Formulation Factor	Physiological Factors
Particle size	pH of formulation	Nasal blood flow
Chemical form	Buffer capacity	Effect of mucociliary clearance
Polymorphism	Osmolarity	Effect of pathological conditions
Molecular weight	Preservative	Effect of enzymatic activity
Lipophilicity	Humectant	-
Dissolution rate	Antioxidant	-
Solubility	Solubilizes	-

2.6. Formulation development in nasal drug delivery :[42,43,44,31,23]

Specific types of dosage forms which are used to deliver formulations into the nose are important in determining the nasal absorption profiles of drugs. Choice of a certain dosage form generally depends on the drug being developed, indication being pursued, patient population, and marketing aspects. Various different nasal dosage forms which have been developed considered reported include the following Specific types of dosage forms which are used to deliver formulations into the nose are important in determining the nasal absorption profiles of drugs. Choice of a certain dosage form generally depends on the drug being developed, indication being pursued, patient population, and marketing aspects. Various different nasal dosage forms which have been developed considered reported include the following Specific types of dosage forms which are used to deliver formulations into the nose are important in determining the nasal absorption profiles of drugs. Choice of a certain dosage form generally depends on the drug being developed, indication being pursued, patient population, and marketing aspects. Various different nasal dosage forms which have been developed considered reported include the following Specific types of dosage forms which are used to deliver formulations into the nose are important in determining the nasal absorption profiles of drugs. Choice of a certain dosage form generally depends on the drug being developed, indication being pursued, patient population, and marketing aspects. Various different nasal dosage forms which have been developed considered reported include the following Specific types of dosage forms which are used to deliver formulations into the nose are important in determining the nasal absorption profiles of drugs. Choice of a certain dosage form generally depends on the drug being developed, indication being pursued, patient population, and marketing aspects. Various different nasal dosage forms which have been developed considered reported include the following

2.6.1 Nasal drops:

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays. Nasal drops, if administered correctly deposit drug throughout the nasal cavity, which offers a larger effective area for immediate absorption than if the drug is delivered in form of a spray. Some drug is certainly deposited on the ciliated regions of the mucosa and is therefore immediately available for clearance.

2.6.2 Nasal sprays:

Nasal sprays are available as squeeze bottles which would not be expected to give reproducible dosing. They are also available as metered dose devices which would be expected to give more reproducible dosing as a mechanical actuation delivers a pre-determined volume to the patient. Thus the dose of drug received by the patient will be dependent on the concentration of drug in the formulation. Nasal region sprays tend to deposit at their impaction site, in the anterior, non-ciliated regions of the nasal cavity where air-flow associated with inspiration is high and mucociliaryclearanceis slow or erratic.

2.6.3 Nasal powder:

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility particles size, aerodynamic properties and nasal irritancy of the

active drug and or excipients. Local application of drug is another advantage of this system.

2.6.4 Nasal gels:

Nasal gels are high viscocity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post nasal drip due to high viscocity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

2.6.5 Nanoparticles:

Recently, much attention has been given to nanotechnology in many areas. Nanoparticle systems are being investigated to improve drug delivery and intranasal drug administration. Nanoparticles are solid colloidal particles with diameter ranging from 1-1000nm. They consist of macromolecules materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4. The low bioavailability obtained can be due to the fact that particles are probably taken up by M-cells in the nasal associated lymphoid tissue and therefore, transported into the lymphatic system and blood stream. In contrast, other studies have suggested that nanoparticle systems may be ideally suited for the delivery of nasal vaccines.

2.6.6 Microspheres:

Microsphere technology have been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustained drug release, prolonging its effect.

2.6.7 Nasal inserts:

Nasal inserts are novel, bio adhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.

2.6.8 Microemulsion:

Recently, there has been an increased interest for the microemulsions, for the delivery of hydrophilic and lipophilic drug as drug carriers because of its improved drug solubilization, longer shelf life, ease of preparation and improvement of bioavailability of poorly soluble drugs. Droplet size of microemulsion is usually in the range of 10-200 nm. A microemulsion system generally consists of four components, a lipophilic phase, a hydrophilic phase, surfactant and co-surfactant. The nature of the components of the system like oil, surfactant, co-surfactant and water, also temperature and pressure which affect the microemulsion systems are known as the formulation variables. Interest in this field is increasing and their applications have been diversified to various administration routes in addition to the conventional oral route. Microemulsion has drawn attention for their use as novel vehicles for drug delivery. Microemulsion systems are also now being widely used for transdermal, ocular, nasal, and intravenous drug delivery.

Table No 1.2: Available nasal products

Drug	Brand	Supplier	Main Indication
Azelastine	Aestelin	MedaPharma	Rhinosinusitis
Beclomethasone	Beconse	GlaxoSmithkline	Rhinosinusitis
Budesonide	Rhinocort	AstraZeneca	Rhinosinusitis
Fentanyl	Instany	NycomedPharma	Pain Management
Mupirocine	Bactroban	GlaxoSmithkline	Eradication of nasal Staphylococci
Nafarelin	Synarel	Roche Laboratories	Management of Endometriosis
nNicotine	Nicotrol Ns	Pfizer	Smoking cessation

3. INTRODUCTION OF MICROEMULSION:[45]

Microemulsion is thus defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution. The essential distinction between normal emulsion and microemulsion is their globule size and stability; the former is 'kinetically stable' whereas the latter is 'thermodynamically stable'. The stability of microemulsion can be influenced by addition of salt, other additives, temperature or pressure. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either water-in-oil (w/o) or oil-in-water (o/w) in nanometer or colloidal dispersions (100 nm). The lower alkanols are called cosurfactants; they lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation of the said microheterogeneous systems. The miscibility of oil, water and amphiphile (surfactant plus cosurfactant) depends on the overall composition which is system specific. Ternary and quaternary phase diagrams can describe the phase manifestations and are essential in the study of microemulsions. In order to gain an understanding of the reasons for microemulsion formation, it is needed first to consider the properties of amphiphiles, such as surfactants in solution. Conventional surfactant molecules comprise a polar head region and polar tail region, the latter having the larger molecular volume particularly in the case of ionic surfactants. On dispersal in water, surfactants self associate into a variety of equilibrium phases, the nature of which stems directly from the interplay of the various inter and intermolecular forces as well as entropy considerations. Surfactants also self-associate in non-aqueous solvents, particularly polar liquids such as alkanes. In this case the orientations of the surfactant molecules are reversed compared to those adopted in

aqueous solution. The reorientations serves to optimize the salvation requirements of the surfactant and minimizes the free energy of the overall system. When surfactants are incorporated into immiscible mixture of oil and water, the surfactant molecules can locate at the oil/water interface which is thermodynamically very favorable. A number of phases can result which may be structured on the microscopic scale, one example of a phase structured on the microscopic scale is an optically isotropic microemulsion phase

3.1 Theories of microemulsion formation:[46,47]

Historically, three approaches have been used to explain microemulsion formation and stability. These are: (i) interfacial or mixed film theories (ii) Solubilisation theories and (iii) thermodynamic treatments. An in depth discussion of these theories are beyond the scope of this review but has been addressed by others. However, an admittedly simplified thermodynamic rationalization is presented below. The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil-water interface and the change in entropy of the system such that,

ΔGf1/4 ΔA - TΔS

It should be noted that when a microemulsion is formed the change in ΔA is very large due to the large number of very small droplets formed. Originally workers proposed that in order for a microemulsion to be formed a (transient) negative value of was required, it is now recognized that while value of is positive at all times, it is very small (of the order of fractions of mn/m), and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion.

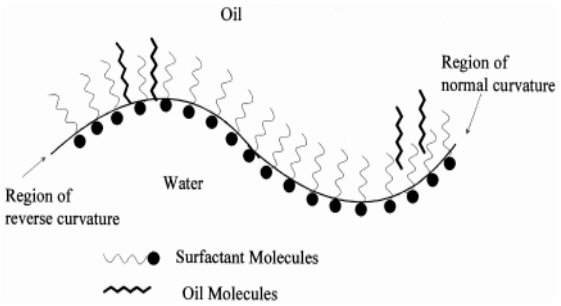

Figure 1.5: Penetration of oil molecules between the hydrophobic chains of the interfacial surfactant monolayer in a bicontinuousmicroemulsion. Note the greater

Extent of oil penetration when the film curves towards water (i.e. in a region of reverse curvature)[48]

Entropy arising from the mixing of one phase in the other in the form of large numbers of small droplets. However, there are also expected to be favorable entropic contra unions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, microemulsification is spontaneous and the resulting dispersion is thermodynamically stable. Qualitatively we know that several factors determine whether a w/o or o/w system is formed. The most likely microemulsion would be that in which the phase with the smaller volume fraction forms the droplets, and indeed this is very often although by no means exclusively the case. By their very nature, o/w microemulsion droplets generally have a larger effective interaction volume than w/o droplets. In the case of ionic surfactants this is attributable to the presence of an electrical double layer at the surface of the o/w droplet which introduces a strong repulsive term. For o/w microemulsions stabilized by a non-surfactant, although there is hydration shell associated with the polar head groups, the predominant repulsive factor can be attributed to steric interactions. Additionally, it is pertinent to note that it is easier to arrange surfactant at an interface with high curvature, i.e., small droplets, if the surfactants tails extend outwards into a continuous oil phase. This is also entropically more favorable as the hydrocarbon tails have more directional freedom. As a result, interfacial tension tends to be lower for a w/o microemulsion than for an o/w microemulsion, thereby making their preparation amore facile process. It should also be remembered however, that while microemulsions are thermodynamically stable there may be kinetic barriers to their formation. As a consequence, the order of component addition may impact on the ease of preparation, and in some cases mechanical agitate on or the input of heat will assist more rapid microemulsification..

3.2 Microemulsion structure:[49]

The structure of microemulsion can be effectively explained by the droplet model where in the droplets of microemulsion are surrounded by interfacial film consisting of both surfactant and co-surfactant molecules. The orientation of these amphiphiles will be different for o/w and w/o microemulsions. The nonpolar portion of these molecules will reside in the dispersed phase of o/w system, while the polar groups protruding in the continuous phase, while the opposite is true for w/o microemulsion.

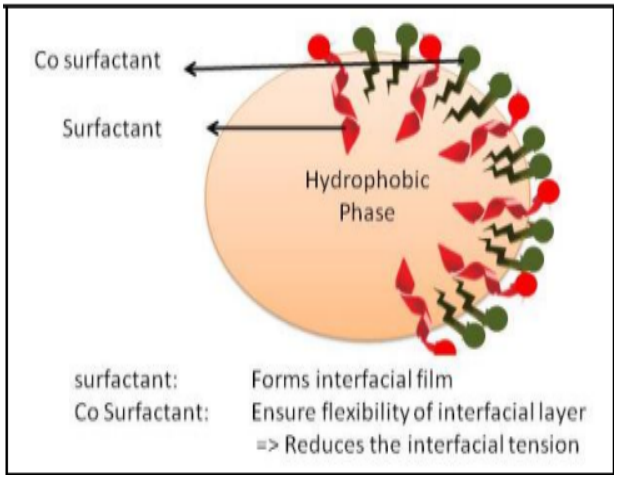

Figure 1.6 :Microemulsion Structure

3.3 Types of microemulsions:[50,51,52]

Micro emulsions are thermodynamically stable, but are only found under carefully defined conditions. One way to characterize these systems is by whether the domains are in droplets or continuous. Characterizing the systems in this way results in three types of microemulsions:

- Oil-In-Water (o/w)
- Water-In-Oil (w/o)
- Bicontinuous

3.3.1 Oil-in-water (o/w):

Oil-in-water microemulsions are droplets of oil surrounded by a surfactant (and possibly co-surfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsions. The monolayer of surfactant forms the interfacial film that is oriented in a "positive" curve, where the polar head-groups face the continuous water phase and the lipophilic tails face into the oil droplets. The o/w systems are interesting because they enable a hydrophobic drug to be more soluble in an aqueous based system, by solubilizing it in the internal oil droplets.

3.3.2 water-in-oil (w/o):

A w/o microemulsion used orally or parenterally may be destabilized by the aqueous biological system. The biological system increases the phase volume of the internal phase, eventually leading to a "percolation phenomenon" where phase separation or where dilution by the aqueous phase is unlikely, such as intramuscular injection or transdermal delivery.

3.3.3 Bicontinuous:

Bicontinuousmicroemulsions, as mentioned before, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration, where upon dilution with aqueous biological fluids, form an o/w microemulsion.

3.4 Formulation considerations and potential ingredients:[53,54]

In general, the phenomenon of microemulsification is mainly governed by the factors such as:

- Nature and concentration of the oil, surfactant, cosurfactant and aqueous phase
- Oil/surfactant and surfactant/cosurfactant ratio
- Temperatue and pH of the environment and
- Physicochemical 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.

3.4.1 Oily phase:

Selection of an appropriate oily phase is very important as it influences the selection of the other ingredients of microemulsions, mainly in case of o/w microemulsions. Usually, the oil, which has maximum solubilizing potential for the selected drug candidate, is selected as an oily phase for the formulation of micremulsions. This helps to achieve the maximal drug loading in the microemulsions. At the same time, the ability of the selected oil to yield systems with larger microemulsion existence region is also important. It is difficult for a single oily component to amalgamate both these requirements. It is known fact that oils with excessively long hydrocarbon chains (or high molecular volume) such as soybean oil are difficult to microemulsify whereas oils with shorter chain (or low molecular volume) such as medium chain triglycerides(MCT), fatty acid esters (like ethyl oleate) are easy to microemulsify. On the contrary, the capacity of solubilization of lipophilic moieties usually increases with the chain length of the oily phase. The choice of the oily phase is often a compromise between its ability to solubilize the drug and its ability to facilitate formation of microemulsions of desired characteristics. In certain cases, mixture of oils is also used to meet both the requirements. For example, a mixture of fixed oil and medium chain triglyceride is used in certain cases to have good balance between drug loading and emulsification. Recently, vitamin E (d-tocopherol) based emulsions are proposed in some investigations mainly due to its solubilizing potential. It has been reported that vitamin E can solubilize API such as itraconazole, Saquinavir and paclitaxel which are difficult to solubilize by using conventional oily components. There are no reports on the vitamin E based microemulsions but there is a great scope to develop such systems. Recently, microemulsions based on medium chain mono- and di-glycerides have also been reported. Medium chain mono- and di-glycerides such as Capmul MCM have much higher solubilization potential than that of the fixed oils and MCT and they are easy to microemulsify.

3.4.2 Surfactants:

Choice of the surfactant is critical for the formulation of microemulsions. The surfactants should favor microemulsification of the oily phase and should also possess good solubilizing potential for the drug. These factors must be considered while choosing a type and the concentration of surfactant. Generally, surfactants of natural origin are preferred over synthetic surfactants, e.g. phospholipids are preferred over synthetic surfactants wherever possible. By and large, the surfactant concentration in microemulsions should be minimal as far as possible irrespective of its nature, origin and type. The choice of the surfactant would also be governed by the type of the microemulsion to be formulated. Low HLB surfactants such as Sorbitan monoesters are preferred for w/o microemulsion whereas high HLB surfactants such as polysorbate 80 are preferred for o/w microemulsion. In several cases, a mixture of lipophilic (low HLB) and hydrophilic surfactants (high HLB) may be required to obtain a microemulsion. Amongst various surfactants are available, Lecithin's, polaxomers and polysorbate 80 are most preferred. Polyethoxylated castor oil derivatives (Cremophore EL, Cremophore RH 40 and Cremophore RH 60) are used in some of the currently marketed co-solvent based formulations. Lecithins are too hydrophobic to form spontaneously the zero curvature lipid layers required for the formation of balanced microemulsions. This is achieved by using auxiliary surfactant like polysorbate 80. Amongst polaxomers, polaxomer 188

should be preferred over polaxomer 407. Polaxomer 407 is known to cause hyperlipidemia on long-term administration.

3.4.3 Cosurfactants:

Most of the times, surfactant alone cannot lower the oil-water interfacial tension sufficiently to yield a microemulsion which necessitates addition of an amphiphilic short chain molecule or cosurfactant to bring about the surface tension close to zero. Short chain length ranging from C2 and C10 and amphiphilic nature of these agents enable them to interact with surfactant monolayers at the interface thereby affecting their packing. Liquid crystalline phases are formed when the surfactant film is too rigid. Cosurfactant penetrate into surfactant monolayer providing additional fluidity to the interfacial film and thus disrupting the liquid crystalline phases. Furthermore, cosurfactants also distribute themselves between aqueous and oily phase, thereby altering the chemical composition and hence the relative hydro/lipophilicity of the system. The short chain amphiphilic nature of ethanol enables formulation of microemulsions with avariety of oily phases and surfactants. The concentration of ethanol should preferably not exceed 10% (v/v). However, in most of the cases, it has been found to be inferior as compared to the ethanol. Alkanediols such as propylene glycol and alkanetriol such as glycerol can also be used as cosurfactant in the microemulsions. Usually, both of them have to be used at a high concentration to produce microemulsions which is attributed to their extreme hydrophilicity.

3.5 Methods of microemulsion preparation:[55]

3.5.1 Phase titration method (water 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 needful approach to study the complex series of interactions that can occur when different components are incorporated in a system. Microemulsion formulation goes along with various association structures (emulsion, micelles, hexagonal, lamellar, cubic, and gel and oily dispersions) depending on the chemical composition and concentration of each component. The understanding of their phase equilibria and demarcation of the phase boundaries bare essential aspects of the study. Pseudo ternary phase diagram is often constructed to find the different zones including microemulsion region, in which each corner of the triangle represents 100% of the one particular component. The region can be separated into o/w or w/o microemulsion by simply considering the composition that is whether it is water rich or oil rich. Observations must be made carefully so that the metastable systems are not included.

3.5.2 Phase inversion method:

Phase inversion of microemulsion occurs on addition of dispersed phase or in response to temperature. During phase inversion physical changes occurs including particle size change that can affect drug release *in vivo* and in vitro. These methods make use of changing the curvature of the surfactant. For non-ionic surfactants, this can be done by changing the temperature of the system by forcing a transition from o/w microemulsions at low temperatures to w/o microemulsions at higher temperatures (transitional phase inversion). At the time of cooling, the system reaches a point of zero curvature and minimal surface tension, promoting the formation of fine oil droplets which are dispersed. This method is also known as phase inversion temperature (PIT) method. Other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone. Also, a transition in the spontaneous radius of curvature can be obtained by changing the water fraction. By adding water into oil phase, initially water droplets are formed in a continuous oil phase. Increasing the water fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point. Short-chain surfactants form monolayers at the o/w interface resulting in a bicontinuousmicroemulsion at the inversion point.

Phase diagram for microemulsion:

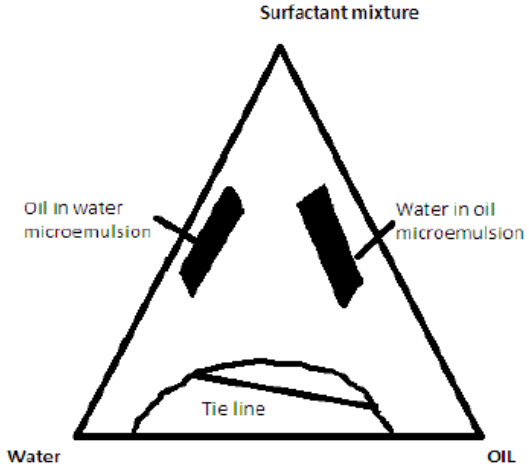

Figure 1.7 : Ternary phase diagram for microemulsion system

3.6 Characterization of microemulsion:[56,57,53]

3.6.1 Thermodynamic stability studies:

To overcome the problem of metastable formulation thermodynamic stability tests are performed. Formulations are centrifuged at 3000 rpm for 30 min. Those formulations which does not show any phase separation are taken for the heating and cooling cycle at temperature of 4ºC and 45ºC for 48 h. The formulations are then observed for phase separation. The formulations which found stable at these temperatures, survived thermodynamic stability are selected for further studies.

3.6.2 Viscocity Measurements:

Viscocity measurements can show the presence of rod-like or worm-like reverse micelle. Viscocity measurements being a function of volume fraction used to determine the hydrodynamic radius of droplets, and interaction between droplets and deviations from spherical shape by fitting results to appropriate models (e.g. for micro emulsions showing Newtonian behavior, Einstein's equation for the

relative viscocity can be used to calculate the hydrodynamic volume of the particles).

3.6.3 Conductance measurement :

O/W microemulsion where the external phase is water are highly suitable for conduction whereas w/o are not, since water is the internal phase. To determine the nature of continuous phase and to identify phase inversion phenomena, the electrical conductivity measurement proves highly useful. Dielectric measurements are a powerful means of probing both structural and dynamic features of microemulsion systems.

3.6.4 Electron microscope characterization:

Transmision Electron Microscopy (TEM) is the most important technique for the study of microstructures of micro emulsions because it directly produces images at high resolution and it can capture any co-existent structure and micro-structural transitions. There are two variations of the TEM analysis is done in which samples are directly visualized after fast freeze and freeze fracture in the cold microscope. The freeze fracture TEM technique is done in which a replica of the specimen is images under RT conditions.

3.6.5 Scattering techniques for microemulsions characterization:

Small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), and static as well as dynamic light scattering are widely applied techniques in the study of microemulsions. These methods are very valuable for getting quantitative information regarding size, shape and dynamics of the components. Static light scattering techniques have also been widely used to determine microemulsion droplet shape and size. In this the intensity of scattered light is generally measured at various angles and for different concentrations of microemulsion droplet. Dynamic light scattering, which is also referred to as photon correlation spectroscopy (PCS), is used to analyze the fluctuation in the intensity of scattering by the droplets due to Brownian motion. The self-correlation is measured which gives information on dynamics of the system.

3.6.6 Rheology:

The rheological properties of microemulsions depend on the type, shape and number density of aggregates present, as well as the interactions between these aggregates. Hence, microstructural changes such as sphere-rod or discontinuous to bicontinuous transitions are reflected in microemulsion rheology. Bicontinuousmicroemulsions exhibit a Newtonian behavior (constant viscocity) at low to medium shear rates but shear thinning is observed at high shear rates, probably due to fragmentation of the bicontinuous structure. Discontinuous microemulsions on the other hand show Newtonian behavior over a wider range of shear rates. However, differentiation of the types of microemulsions or identification of the structure of the microemulsion cannot be done purely on the basis of rheological data, because this macroscopic property is not sensitive enough to detect subtle microstructural changes such as the transformation of microemulsion to a wormlike micellar phase induced by temperature. Hence, rheometry has most often been used in combination with other techniques in the characterization of microemulsions. For example, it has been used in conjunction with SANS and a phase study to measure the percolation threshold and nanostructure of microemulsions containing a polymer and silica nanoparticles.

4. CONCLUSION

Microemulsion have proved to be useful formulations on commercial scale for nasal delivery of hydrophobic drugs. With the appropriate selection of excipients, it is possible to design a nasal microemulsion with desired characteristics such as controlled release. Microemulsion 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 disorders.

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