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NanoemulsionswithIntranasal Delivery:AReview

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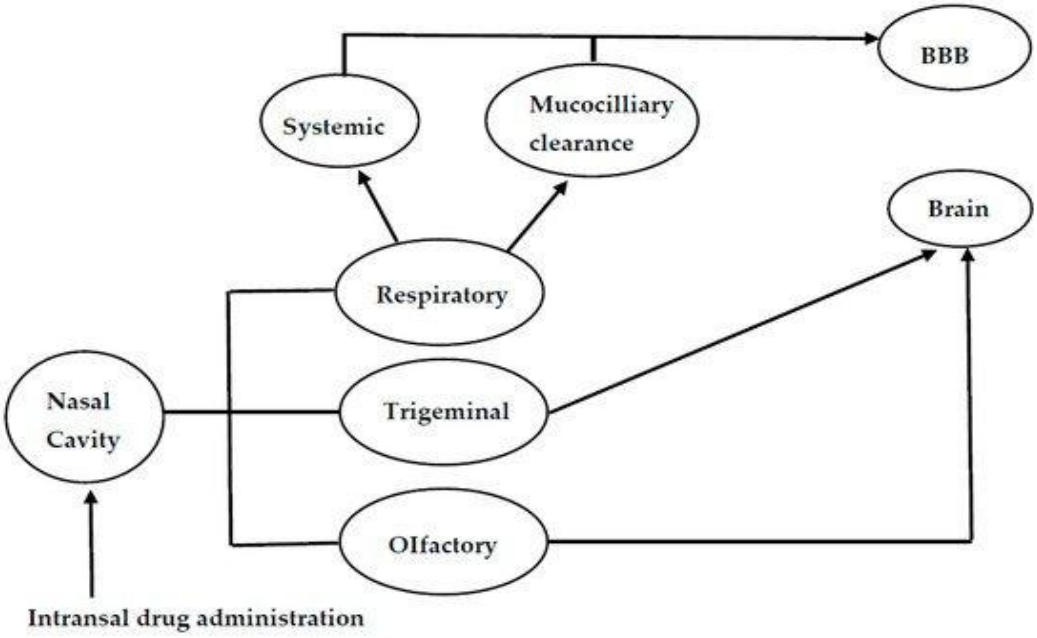
Abstract
In order to resolve the significant disadvantages in the traditional delivery system, new methods of drug delivery are developed. Nanoemulsion is a nano-sized emulsion developed to further increase the availability of active medicament. These are all the thermodynamically steady isotropic system under which two immiscible fluids are combined with a co-factant as well as surfactant emulsifying agent. Hence, nanoemulsionshave advantage of increasing biovailability by avoiding first pass effect ,low solubility and enzymatic degradation.Through nasal course. the medication can get straightforwardly along the trigeminal nerves and olfactory nerves Nanomedicine comprises of emulsion [mostly oil in water] one surfactant or co-surfactant having size measurements [100nm to 300nm or less] with high surface area. Such nanoemulsions have advantage of effectiveas, non-irritant, non-invasive, compared to conventional drug delivery

Keywords: olfactory pathway, nasal mucosa; nose-to-brain delivery; nanoemulsion; brain targeting; Blood-brain barrier

1. INTRODUCTION

BBB, that will not allow the passage of most drugs. By using a nose-to-brain delivery method, BBB may be bypassed. It is non-invasive method of drug delivery. Various nose-to-brain drug delivery technologies have been implemented. The nasal cavity is closely connected to the CNS which indicates designing nasal formulations targeted at brain medicines. Designing and processing nasals formulation includes designing polymeric pharmaceutical platforms capable to cooperate with nasal mucosa: Nasal formulation should have bioadhesion and penetration ability which is a great challenge in the drug field targeted delivery.

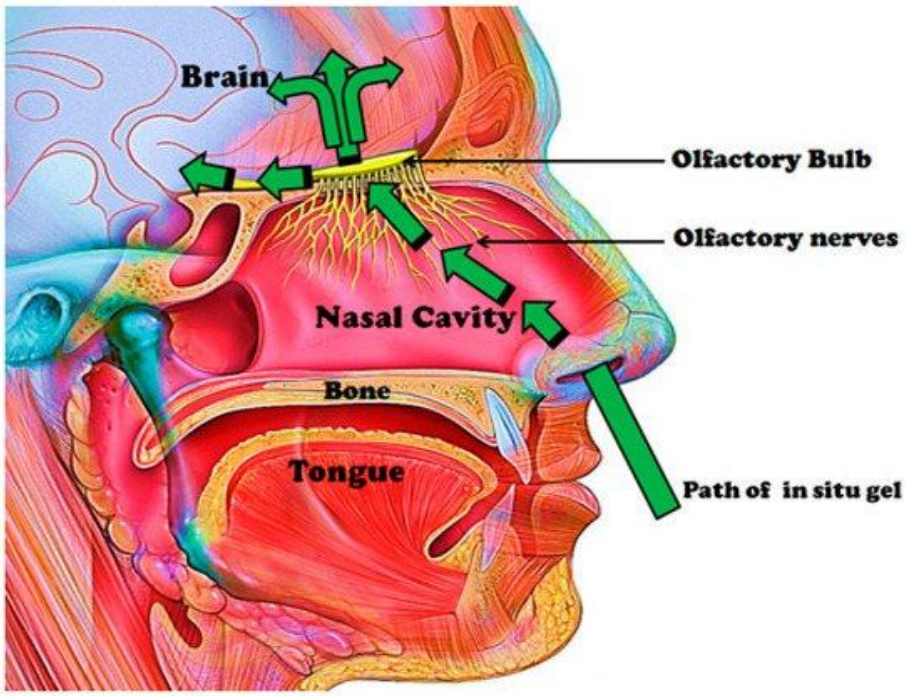
Process of the transfer of drug to brain via nose:



The Blood Brain Barrier (BBB) plays a part in defending against infectious agents and thereby restricting therapeutic acceptance. The first-pass effect is circumvented and bypassed by nasal administration of drugs. The drug enters the brain immediately through the trigeminal and olfactory nerves in the upper part of the nasal cavity through the nasal path. A mucoadhesive polymer like chitosan may be applied to the formulation in order to impair rapid nasal clearance. NEs offers promising formulations in helping delivery ofdrugs into the brain through the intranasal route of administration.. This review aims in highlighting the present situation in literaturewith particular attention to recent publications considering the uilization of NEs for nose-to-brain targeting,.

Drug is administerd to brain through intra-cerebroventricular or intraparenchymal injections route, mini-pump intracranial delivery, catheter inflammation, centred ultrasound methods and external electromagnetic champ methodologies. These are all very risky and invasive procedures, though, particularly because of the necessary for operating surgery. For that cause, techniques are built to circumvent the BBB for the transport to the target position of active substances.

Nose-to-brain drug delivery is a non-invasive, **painless**, administration route, which may be utilized for delivering therapeutic agents into the brain throughout bypassing the BBB. Despite their many benefits, the transmission of medicines from nose to brain is restricted because of enzyme oxidation into the mucosal surface of sensible pharmaceutical items, a high degree of clearance and nasal anatomy restrictions (for example mucociliaryclearance, limited surface area of the olfactory mucosa, small volume, etc.). The proper nature of nose-to-brain formulations should appropriate these issues.

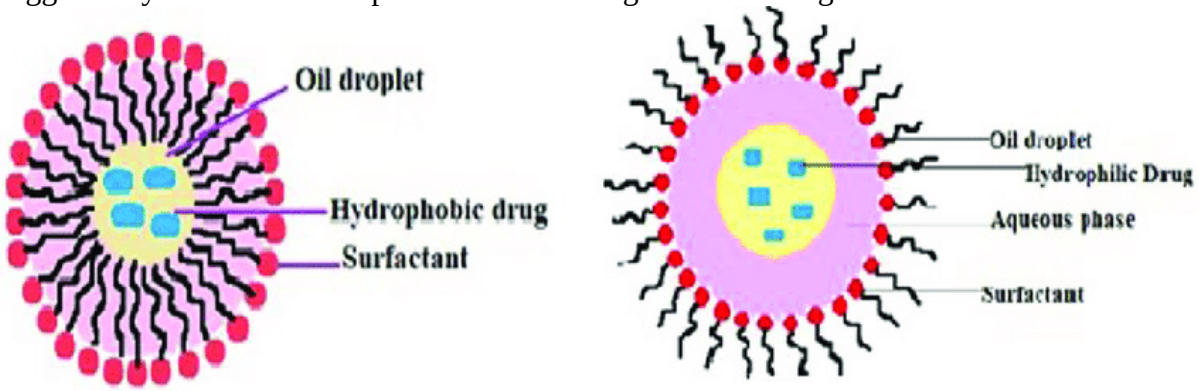


The nose as a route for the administration of drugs:

Nanocarriers are designed for preparing nasal preparations which are able for targeting the brain, and is made of lipid-based as well as polymer-based nanoparticles. Nanocarers show more attention to nose-to-brain distribution in the liquid dispersed structures representing NEs.

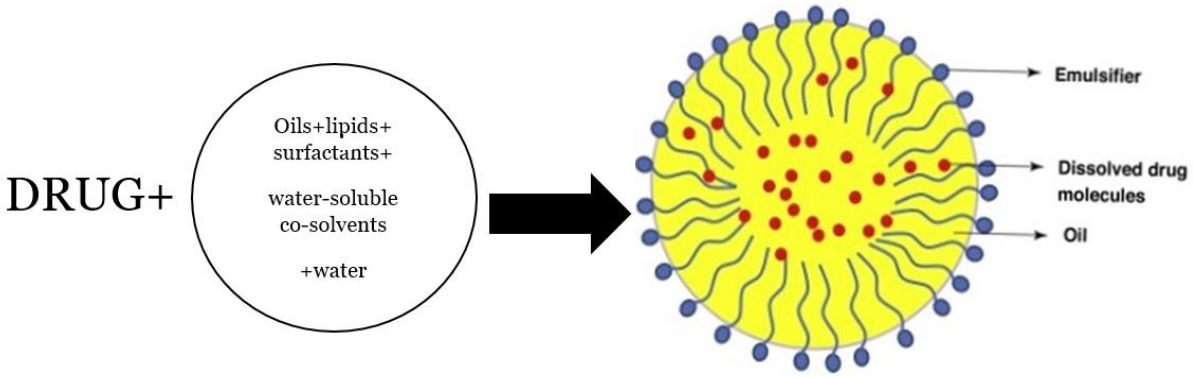
Nanoemulsions in brief

Nanoemulsions are water-in-oil or oil-in-water dispersions of two immiscible liquids stabilized utilizing proper surfactant, with a mean 100nm droplet diameter, NEs have either a transparent or from transparent to milky white appearance because droplets size is suggestively smaller as comapred to the wavelength of visible light



Composition of nanoemulsion: Various components which effects the stability as well as formation, along with NEs' functional properties are refractive index, phase behavior, density, viscosity, as well as interfacial tension of the oil phase. Water form, water-soluble co-solvents, surfactants, lipids, Oils, and NE triglycerides ingredients for example tri-, di-, or mono-acylglycerols, free fatty acids, mineral oils, vegetable oils, etc are included in the formulation of NEs. The selection of oil is based on the solubility of the drug in general. For the production of NE, oil phases that have a huge load of medicines are usually used.

Emulsifiers reduce the interfacial tension resulting in formation of small and stable Commonly employed emulsifier are Lecithin (phosphatidylcholine), sodium deoxycholate (bile salt), polyoxyethlene sorbitan monolaurate and sorbitan monolaurate
In the preparation of NE, Emulsifiers are usually utilized stabilizers as well as the surface active molecules for protecting small droplets. The emulsifiers also helps to prevent coalescence as well as collision among the droplets and rises the Nes' kinetic stability. In the NEs preparation, emulsifier are used as a surfactant but lipids along with proteins were also used. Surfactants such as polysaccharides (gums, starch derivatives), casein, and poly-ethylene-glycol (PEG)-containing block copolymers are also proposed for NE
For stabilization of NEs. Co-surfactants, for example glycerine, ethanol, propylene glycol, ethylene glycol, and polyethylene glycol may be utilized.
The aqueous phase of a NE is made up of co-solvent as well as polar solvent. Adding stabilizer agent to NEcan prevent breakdown due to gravitational separation, coalescence, flocculation, and Ostwald ripening.



2. METHODOLOGY

Different techniques can be used to generate nanoemulsions into two broad categories
1. High energy methods
2. Low energy method

1. High energy method:

High energy methods for the formulation of NE are commonly used. Large droplets are changed to nano-sized droplets and NEs with great kinetic energy are produced by mechanical energy. The mechanical devices including microfluidizer, ultras nicators, and high-pressure homogenizers are used. Great controls for rheology, stability, and color of the emulsion is achieved by these methods
Methods of high energy

- Ultra-Sonification
- Micro fluidization
- High-pressure homogenization

1.1 High-Pressure Homogenization:

A high-pressure homogenizer is used to create very low particle size nanoemulsions (up to 1nm). It is accomplished by pressing the mixture to a very low-pressure inlet aperture (500-5000 psi), which allows the substance to be exposed to intense turbulence and hydraulic

shearing, which results in very small emulsion particles. The shaped particles reveal a liquid lipophilic core segregated by a single layer of phospholipids from the surrounding aqueous phase. In order to achieve optimized methodology according to system variables, could be analyzed for optimizing the formulation.
Impact of Homogenization Pressure and Number of Homogenization cycles. The only downside is high energy consumption and increased emulsion temperature during processing.

1.2 Ultrasonication:
Different research papers report on the preparation of nanoemulsion to unitize an ultrasonic sound frequency for a decrease of the droplet scale. The key cause of ultrasonically induced impacts is cavitation. The development and fall of vapor cavities in moving fluid is cavitation. Cavitation This voracity arises as local pressure decreases to the steam pressure at the fluid temperature due to changes in local speed. The collapse of these cavities causes powerful waves of shock to radiate across the solution close to the rays of the face of the tip, fracturing the dispersed liquid, since cavity dissipates power in a small frequency ultrasonic system the most critical mechanism of power dissipation, these changes in the speed of navigation could be directly related to energy density changes. The device also utilizes a water jacket to regulate the maximum temperature (Bhatt and Madgav, 2011).

1.3 Micro fluidization:
The microfluidizer is a device which is fitted with a positive displacement high-pressure pump (500-20000psi), that forces the substance via the chamber of interaction containing small channels known as channels of micro. The emulsion moves via the fine particles in the sub-micron range through the microchannel in a zone of impingement. The oily and aqueous phases are mixed and transformed into a coarse emulsion inline homogenizer to yield. The gross emulsion is moved to the micro-fluidizer to achieve a steady nanoemulsion. The required particle size is achieved by passing the emulsion repeatedly by micro fluidizereFoltration of the emulsion is done with a nitrogen filter to extract large droplets which leads to the uniform emulsion of nano (Hadgraft, 2001).

2. Low energy method:
These methods are more power efficient as they require less energy because these approaches utilize the interior chemical energy of the system. There are two methods used. Self-emulsification and Phase inversion emulsification. But these methods are not preferred in food-grade as a high concentration of surfactant is required that impacts food safety

- Method of the emulsification inversion process

(i) Emulsion inversion point
(ii)Phase inversion composition
(iii) Phase inversion temperature

- Self-nano emulsion method

2.1 Phase inversion method:
Phase transitions produced by the emulsification pathway produces chemical energy which results in fine dispersion. The structure of the emulsion is varied and constant temperature is preserved or conversely and process transition are produced. The phase inversion with an elevated temperature leads to chemical changes of surfactants of polyoxyethelene by degrading the polymer chain with the temperature (Hussan, 2011).

2.2 Self-nano emulsification method:

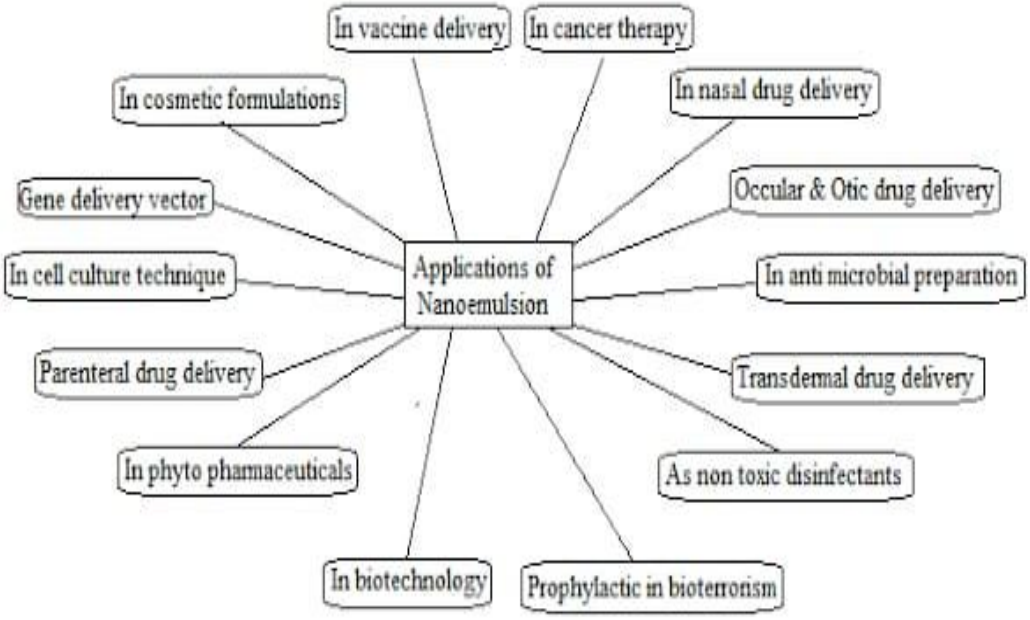
Nanoemulsion formation is accomplished in the auto emulsification procedure without altering the surfactant's spontaneous curvature. Co-solvent molecules and/or surfactant spread easily from the dispersed process to the continual level, leading to turbulence and nanosized emulsion droplets. The process of self-emulsification is called the spontaneous method of emulsification (Solans and Solé, 2012; Solans et al., 2016). Self-nano emulsifying drug delivery system (SNEDDS) is focused on the auto-emulsification phenomenon with co-surfactants(co-solvents) or hydrophilic surfactants and lower lipid content (Agrawal et al., 2012). SNEDDS could be described as co-surfactant, surfactant, isotropic oil, and pharmaceutical combination. If diluted in vivo with aqueous fluids, this mixture forms a fine and visually transparent O/W nanoemulsion and helps with gentle agitation through the digestive motility of the intestine and stomach (Khan et al., 2015; Bandyopadhyay et al., 2014).

Difference between nanoemulsion and microemulsion:

Sr.No.	Property	Nanoemulsion	Microemulsion
1.	Droplet size	20-500 nm	5-100 nm
2.	Method of preparation	Low-energy method and High-energy method	Low-energy method
3.	Stability	Thermodynamically stable	Kinetically stable
4.	Quantity of stabilizing agents	Less co-solvents, co-surfactants proteins, and polysaccharides used	Sufficient co-solvents and co-surfactants used

Uses of Nanoemulsions:

- NEs have advantages of drug stability and/0r drug solubility under physiological conditions such as hydrolysis, enzymatic degradation, pH, and oxidation at the mucosal level.
- Hydrophobic drugs can dissolve in the oily phase and nanoprecipitation occurs as they are extracted from the NE (in the oil phase) as they come into contact with the surrounding aqueous environment. It results in the creation of particles with a very high surface and a major improvement to the rate of medication dissolution.
- NEs may be used to conceal disagreeable substance tastes.
- NEs could be developed in various types of dosage like sprays, liquids, foams, gels, and creams etc., could be delivered through oral, parenteral, and ocular routes as well as the nasal route.



General overview of nanoemulsion for nose-to-brain delievery

Some nanoemulsiondrugwhich are given via nose to brain:

Sr. No.	NE drugs	Type	Constituent	Oily Phase/emulsier	Diseases
1.	Risperidone	Antipsychotic	API+capmul MCM+tween 80	CapmulMCM,tween 80	Schizopherina, Bipolar disorder
2.	Olanzipine	Antipsychotic	Api+chitosan	Chitosan	Schizoperina
3.	Ergoloid mesylate	Antiaginin g	Api+egg lecithin	Egg lecithin	Used in prevention of aging
4.	Selegline	MAO-B Inhibitor	API+tween 20	Tween 20	Parkinson disease
5.	Thymoquinone	Anti-cancer, Anti-inflamatory	API+carbitol(cosurfactant) +tween 20 (surfactant)	Both	Cerebral ischemia
6.	Zolmitriptan	Anti-migraine Selective serotonin receptor	API+chitosan[mucoadhesive]	Chitosan	Migraine

		agonist			
7.	Nimodipine	Calcium channel blocker	API+sodium alginate+sodium CMC+labrasol+transcutol	CapmulMCM,carbopol chitosan	Cerebrovascular spasm,senile dementia

[1] Risperidone:-

Risperidone is an anti-psychotic agent in the group of benzisoxazole derivative drugs [M Kumar et al.] Due to the first stage hepatic metabolism, the drug is also available in oral solutions and tablets that are characterized by a drawback of poor bioavailability. There are several side effects of Alsosystemic oral administration.

Resperidone NEs are made with capmulMCM that is a mono-diglyceride of medium chain fatty acids (primarily capric and caprylic) as an oil phase (8%w/w) as well as tween 80 as a surfactant. By adding chitosan (0.50 percent), Resperidone mucoadhesive NEs has been prepared

Terminologies: -

- **CapmulMCM:-** Capmul is a mono- and diglyceride emulsifier products that is prepared by glycerolysis of specific fats, oils and partitioned vegetable fatty acids.
- **Tween 80(polysorbate 80, polyoxyethylenesorbitan monooleate**):- Non-ionic surfactant is commonly used in pharmaceutical food, products and cosmetics as emulsifier.
- **Chitosan**:- Chitosan is a polysaccharide that is non-toxic, biodegradable, antimicrobial and biocompatible. Chitosan NE have transparency, thermodynamically stability, good permeability, mechanical strength, and dispersibility. It is composed of (acetyl-d-glucosamine and beta-linked d-glucosamine). It is manufactured by treating alkaline substances like sodium hydroxide in chitin shells of shrimp and other crustaceans.

[2] Olanzipine:-

It is a second-generation antipsychotic agent (used in treatment of schizophrenia also mood stabilizer in bipolar disorder) with broad efficacy. Presence of chitosan helps in enhancing nasal retention time. It is a mucoadhesive agent in nasal formulation. mucoadhesive polymers are water soluble and water insoluble polymer was prepared by [M Kumar et al.]

[3] Ergoloid mesylate

Ergoloid mesylate contains methane sulphonate salts of three alkaloids dihydroergocryptine, dihydroergocristine and dihydroergocornine. The primary emulsifier was egg lecithin. [Yu et al] Nasal administration of this drug has been contrasted with drug solution nasal and iv administration. Compared to those obtained with the iv administration, the region under curve and absolute bioavailability in the CSF were higher after intranasal administration of the submicron emulsions.

[4] Selegiline:-

With neuroprotective and antioxidant effects **monoamine oxidase b inhibitor** used for oral parkinson therapy. However, because of its low solubility in water and its metabolism of the first pass the drug has poor bioavailability (10 percent). To overcome this problem NE is prepared. In a mixture of sefsol 218 and grape seed oil, the selegline indicated highest solubility, tween 80, as a surfactant. [M Kumar et al.]

Treatment:- **Parkinson disease**(MAO-B enzyme breakdown dopamine into free radicals of dopamine)

[5] Thymoquinone:-

Thymoquinone is a phtochemical obtained from the plant nigella sativa.it has been reported for its analgesic, anti-cancer, anti-inflammatory and anti-pyretic. This is primarily used in cerebral ischemia (condition in which the blood supply into the brain is inadequate to satisfy the requirement for metabolism. It causes a low supply of oxygen and cerebral hypoxia, resulting to brain tissue death or ischemic stroke/brain damage).

Ionic gelation method is used to prepare NE with tween 20/labrasol as surfactant, oleic acid as oil and carbitol as co-surfactant. Chitosan is used as a mucoadhesive polymer. It is used in the treatment of cerebral ischemia. This emulsion shows a better bioavailability and therapeutic effect. [Pandey et al.]

[6] Zolmitriptan:-

It is a selective serotonin receptor agonist. It is a triptan used in the acute treatment of migraine Zolmitriptan works by the blood vessels narrowing across the brain. Reduce even nausea, sound and light sensitivity, tr headache pain, as well as other signs of migraine. [Mc Keage et al.]

Zolmitriptan serves as an oral tablet that disintegrates. Oral treatment has various disadvantages, like headache recurrence, slow onset action, poor bioavailability [40 percent], and a limited half-life. Therefore, there is a need of NE with this API so that enhancement of bioavailability of this drug can increase and cross the BBB.

Zolmitriptan mucoadhesive NEs have been made and the zeta potential, size of particle, morphological and in-vivo permeation by the nasal mucosa were characterised. In addition to chitosan as a mucoadhesive agent the residence time and the zeta potentiality of the formulation is increased by 0.3 percent with no significant impact on globule size. Thus, the region under curve is wide and t-max in the brain is shorter than nasal or intravenous solutions.

[7] Nimodipine:-

For oral therapies, Nimodipine is used as a dihydropyridine calcium channel blocker, but it has many issues, such as low oral bioavailability [5 to 10 percent] because of low water solubility and subsequently low brain concentration of medication which is due to first pass metabolism. Furthermore, nimodipine is a p-glycoprotein substrate. This drug efflux mediated by p-glycoprotein can be a source of low concentrations of brain drug. So, NE is prepared to overcome this problem. Mucoadhesive polymers are used such as [sodium cmc, carbopol 934 p, sodium alginate and chitosan] are used. Pluronic f 68 as well as Pluronic f127 used as gelling substance. The drug has dissolved as oil in capmul MCM, using transcutol p as co-surfactant and labrasol as surfactant. Seniline dementia and cerebrovascular spasm is treated with Nimodipine. [Pathak et al.]

3. CONCLUSION

Nanoemulsions for nasal administration which increase bioavailability of drug to CNS a valuable approach for the supply of nose-to-brain drugs to treat neurotic diseases. However, clinical trials of these formulations also need to be done in clinical practise to show their adequacy. We know that cyclodextrins may be used in the formulation have ability to cross

the BBB preparation, administered by nasal or oral/parenteral path. The existence of chitosan as a complementary excipient has a double role, as it is mucoadhesive and has penetration properties that improve the nasal mucosa. Moreover, the surfactants present in the nanoemulsion helped in enhancing drug permeability by interacting with olfactory and trigeminal pathways.

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