JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

NANOEMULSION: PRESENT PROSPECTS AND APPLICATION IN DRUG DELIVERY

Gyati Shilakari [1]* B. Srilatha[1], , T.K.T.S, Krishna[1], B. Sadhana[1]
[1] Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Hyderabad, India

ABSTRACT

Nanoemulsion represent a cutting-edge approach for enhancing the bioavailability of both hydrophobic and hydrophilic drugs, as well as those susceptible to high first-pass metabolism. These colloidal systems, typically comprising oil, surfactant, and an aqueous phase, demonstrate isotropic clarity and either thermodynamic or kinetic stability, with droplet sizes ranging from 10 to 500 nanometers. The utilization of nanoemulsions (NE) facilitates sustained or controlled release of drugs and bioactive ingredients, effectively overcoming challenges associated with drug instability or poor solubility. These systems are primarily prepared using either high-energy or low-energy methods. Characterization and assessment of NE involve various parameters including particle size, zeta potential, and refractive index, among others. NE can be administered through different routes such as orally, topically, intravenously, intrapulmonary, intranasally, and intraocularly. Furthermore, they can be formulated into a variety of dosage forms including gels, creams, foams, aerosols, and sprays, employing cost-effective standard operating procedures. This review concentrates on recent advancements in nanoemulsion development and its final application.

Keywords: Nanoemulsion, preparation methods, characterization, applications.

INTRODUCTION

Modern drug delivery systems have evolved significantly over the past few decades, aiming to improve the therapeutic efficacy, safety, and patient compliance of pharmaceuticals. These systems encompass a wide range of technologies designed to control drug release, targeting, and absorption in the body. Nanotechnology has revolutionized drug delivery by providing innovative platforms for improving drug solubility, stability, targeting, and controlled release. Nanoemulsion preparation is an advanced delivery system used for drugs, biologically active, and genetic substances that have release problems. Since 40% of chemical substances are naturally water-insoluble, the delivery of these hydrophobic substances is a challenge for their delivery. [1]

NANOEMULSION

NE can be defined as a colloidal dispersion consisting of an appropriate ratio of oil emulsified in the aqueous phase, surfactant, and co-surfactant. NE is clear, thermodynamic, and kinetic stability. It is used in pharmaceutical industries because it increases the solubility of lipophilic drugs and leads to bioavailability improvement of these substances by particle size reduction of powdered drugs and nano-sized droplet formation with range (10-100 nm). NE has several advantages over other dosage forms including

a. Increase the rate of absorption
b. Eliminates variability in absorption
c. Helps to solubilize lipophilic drug
d. Provides aqueous dosage form for water-insoluble drugs
e. Increases bioavailability
f. Rapid and efficient penetration of drug moiety protects from hydrolysis and oxidation

TYPES OF NANOEMULSIONS:

Nanoemulsions are various types such as O/W, W/O, and Multiple emulsions as shown in fig.1

1. **Oil in Water nanoemulsion (O/W):** This kind of nanoemulsion disperses oil throughout the continuous aqueous phase.

2**. Water in Oil nanoemulsion (W/O)**: Water droplets dispersed throughout the continuous oil phase in this kind of nanoemulsion.

3.Two-phasenanoemulsions

In this kind of nanoemulsion, the oil and water phases function as one continuous unit. The bi-continuous nanoemulsions are depicted in fig. 1. The interface is stabilized in the three types of nanoemulsions mentioned above by using the right ratio of surfactants and surfactants themselves. Emulsions and nanoemulsions vary primarily in that the former have intrinsic thermodynamic instability and will eventually phase separate, even though they may show good kinetic stability. Emulsions and nanoemulsions differ significantly in appearance, with the former being hazy and the latter being clear.[2]

Comparison aspects of Emulsions, Microemulsion and Nanoemulsion:

Emulsions, Microemulsion, and nanoemulsion are compared with various parameters as displayed in table no1.

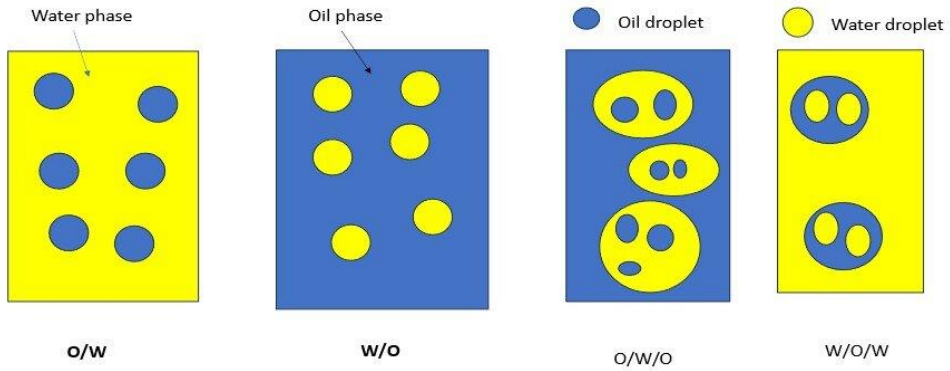

Fig No.1 Types of Nanoemulsion

Table o.1 Difference between nanoemulsion, emulsion, and microemulsion

Parameters	**Emulsion**	**Microemulsion**	**Nanoemulsion**
Type of dispersion	Coarse	Colloidal	Colloidal
Formation	Require energy	Spontaneous	Require energy
Composition	Require more surfactant	Require a less amount of surfactant and co-surfactant combination	Require less surfactant
Visual characteristic'			
Consistency	Fluid/semi-solid	Fluid	Fluid
Turbidity	Turbidity	Transparent	transparent
Particle size	-	below 100 nm	~200 nm

OBJECTIVES: NEs were prepared with many objectives as shown in fig no 2

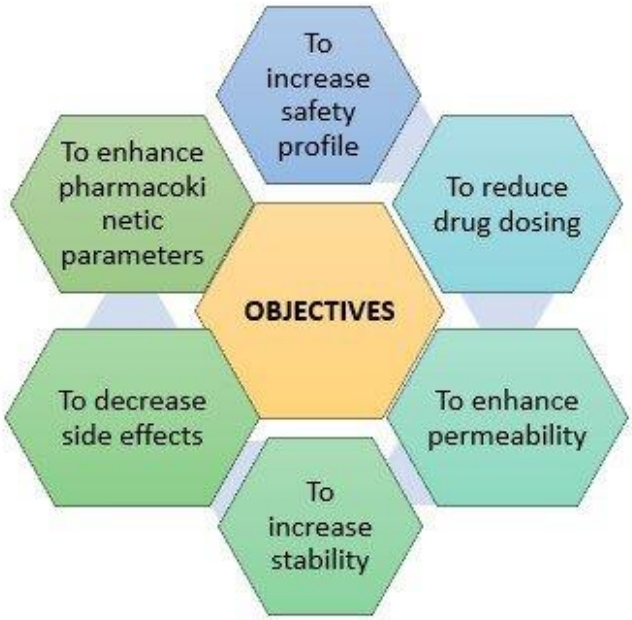

Fig no.2 Schematic representation of objectives of nanoemulsion

DISADVANTAGES

a. The only disadvantages of this technique are **high energy consumption** and an increase in the temperature of the emulsion during preparation.

b. Expensive process

COMPONENTS OF NANOEMULSIONS: Nanoemulsions mainly consist of 4 components

- **OILS**
- **SUFACTANTS**
- **CO -SURFACTANTS**
- **AQUEOUS PHASE**

1.Oil

The oil used in the nanoemulsion formulation has been regarded as a critical element when the drug is administered as a droplet in the oily phase and transmitted in the aqueous phase. The oil chosen must dissolve the compounds used in the dosage form and work effectively with the other ingredients in the nanoemulsion to increase the proportion of the medicine loaded. Natural, semi-synthetic, or synthetic oil can be utilized in nanoemulsion.

2. Surfactant (surface-active agent):

Surfactants are compounds that reduce surface tension or interfacial tension that exists between a liquid and a solid. Depending on the hydrophilic-lipophilic balance (HLB) ratio, surfactants can function as emulsifiers, wetting agents, foaming agents, detergents, or dispersants. Surfactant is used in the preparation of NE to stabilize the system; the type of surfactant used depends on the type of nanoemulsion being generated. For o/w nanoemulsion, hydrophilic surfactants with an HLB value greater than 10 are utilized, whereas hydrophobic surfactants with an HLB value less than 10 are utilized for w/o nanoemulsion. The application of surfactant mixtures with different HLB values, which, when diluted with water, generate a stable nanoemulsion.

3. Co- Surfactant

When the surfactant was unable to reduce the interfacial tension between oil and water, these components were added to the nanoemulsion formulation. Additionally, by penetrating a surfactant monolayer and disturbing its

crystalline liquid phase, it provided some fluidity to the interfacial tension of the surfactant when it exhibits high stiffness.[3]

Table no.2 Components of nanoemulsions

Components	Examples
Oils	Capmul MCM, Capryol 90, Captex 355, Oleic acid, Peanut oil, Caster oil
Surfactants	Labrasol, Kolliphor Rh 40, Cremophor EL, polyethylene glycol, Polysorbate 20, Polysorbate 80.
Co-surfactants	Transcutol HP, PEG 300, PEG 400, ethanol, propanol,
Emulgents	Natural lecithin, castor oil derivatives
Tonicity modifiers	Glycerol, Xylenol and Sorbitol
Anti-oxidants	Ascorbic acid and tocopherol

Following factors should be taken into account during formation of a nanoemulsion

- The dispersed phase molecules need to be soluble in the continuous phase;
- a flexible interface has to form;
- the surfactant needs to be soluble in the continuous phase and components must be added carefully.[4]

Formulation Techniques of Nanoemulsion

As NEs are non-equilibrium systems, preparing them requires significant amounts of energy, surfactants, or both. There are numerous methods for fabricating nanoemulsion, which can be categorized as high-energy or low-energy methods. The high-energy approach breaks the water and oil phase to achieve nanoemulsion by using mechanical devices to generate significant disruptive forces.
Using the low-energy approach, tiny droplets are formed by utilizing internal energy that has been stored. Emulsions can be produced by adjusting process variables such as composition, temperature, and others that impact the hydrophilic-lipophilic balance (HLB). The manufacture of NEs requires more energy than that of a macroemulsion. Surfactants are essential for reducing the surface tension at the oil-water contact. Non-ionic surfactants have a higher surface tension-reduction capacity than polymeric surfactants. However, compared to low-energy methods, high-energy methods require less surfactant, making them better for food-grade emulsion. The methods used for preparing NEs drug delivery systems are numerous and exhibit significant overlap. Several methods to develop NEs drug delivery systems have been categorized based on self-emulsification, phase inversion type, and energy needs.[1]

1.High pressure homogenization:

Manufacturing of NEs needed a high shear force, this technique uses a high-pressure homogenizer, also known as a piston homogenizer, to produce nanoemulsions with extremely small particle sizes (up to 1 nm). This method involves applying pressures between 500 and 5000 psi to a mixture to drive it through an aperture as shown in fig 3. The endproduct undergoes additional processing that includes hydraulic shear and strong turbulence, producing an emulsion with incredibly small particles. This is the most effective way to manufacture NEs; however, the main disadvantage of this technique is that it requires an excessive amount of energy and causes the emulsion's temperature to rise while processing. Larger runs of homogenization cycles are also necessary to get lower particle sizes. [5]

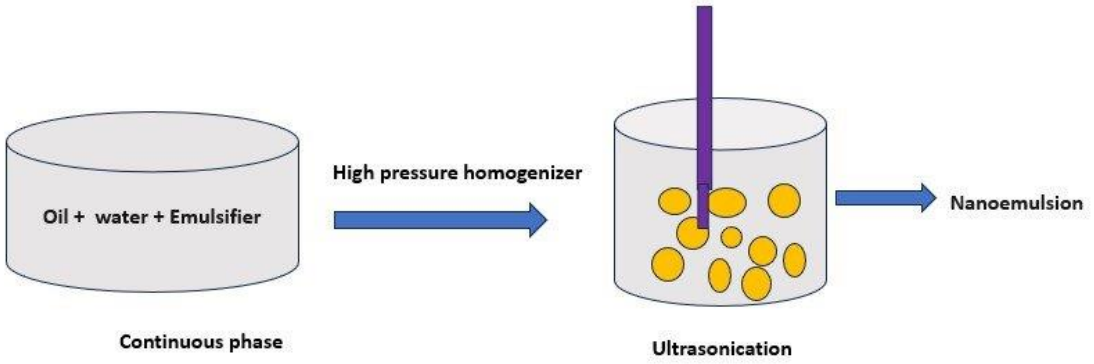

Figure No 3: High pressure homogenization

2.Micro-fluidization:

The pharmaceutical industry uses micro-fluidization the most frequently to obtain fine emulsions. This technique makes use of a microfluidizer, a device that generates high pressure (Figure 4). High pressure throughout the procedure compels the macroemulsion to pass through to the interaction chamber, allowing to produce nanoemulsions containing particles in the submicron range. To acquire the appropriate particle size, the procedure can be repeated numerous times while adjusting the operating pressure to produce uniform nanoemulsion generation.
The micro-fludizer's nozzle, also known as the interaction chamber, is where crude emulsion jets from two opposing channels collide. A pneumatically powered pump that can compress air to pressures of up to 650 MPa provides the crude emulsion with mobility. Due to the high pressure, the crude emulsion stream must pass via tiny channels, and a significant amount of shearing force is produced when two opposing channels collide. Therefore, fine emulsions are formed with the support of this force [6].

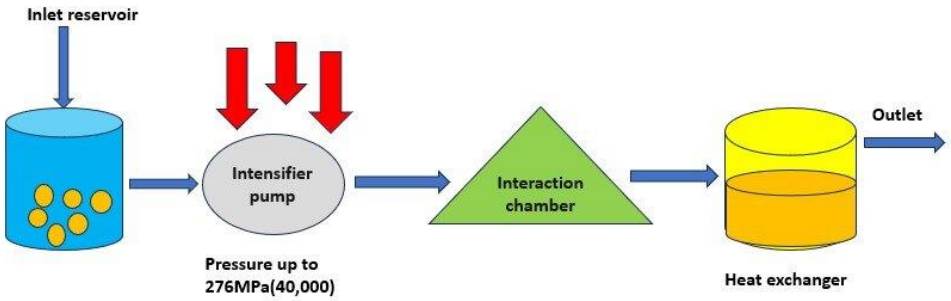

Figure No. 4 Micro fluidization process

3. Ultrasonication:

The ultrasonic emulsification process involves two mechanisms. First, the oil phase disperses as droplets in the continuous phase due to the interfacial waves produced by the acoustic field. Second, the pressure changes of a single sound wave caused by ultrasound induce acoustic cavitation, which results in the production and

collapse of microbubbles, respectively. In this manner, massive amounts of intensely focused turbulence are produced, leading to micro implosions that break big droplets into sub-micron sizes (Zhang, 2011).

This approach involves shaking a solid surface at frequencies of at least 29 kHz to agitate the premixed macroemulsion. High-power ultrasonic devices that break up droplets include pointed tips and focusing horns, which produce severe shear and cavitation. Observations show that majority of ultrasonic systems.

For this reason, recirculation of the emulsion through the high-power zone is required to ensure that all droplets experience the highest shear rate. Furthermore, emulsions with consistent droplet size at diluted concentrations can be obtained by repeatedly performing this kind of recirculation. The most important factors influencing homogenization efficiency are phase viscosity, emulsifier type, and amount.

Thus, for manufacturing nanoemulsions with fine droplets, these characteristics must be optimized. However, because sonication techniques have the potential to cause lipid oxidation, polysaccharide depolymerization, and protein denaturation, there are certain worries about them.[7]

LOW ENERGY METHODS:

1. Spontaneous Emulsification:

Initially, a homogenous organic solution is prepared, consisting of oil, a lipophilic emulsifier, and a water-soluble cosolvent, along with hydrophilic emulsifiers. Subsequently, an o/w nanoemulsion is produced through continuous magnetic stirring. Finally, the aqueous phase is extracted using a reduced evaporation pressure process**[8].**

2. Phase inversion method:

The release of chemical energy during emulsification phase transitions facilitates the formation of fine dispersion. By either maintaining a constant temperature while adjusting the composition and keeping other parameters constant or by maintaining a constant composition while adjusting temperature and keeping other parameters constant, the desired phase transitions can be achieved. The concept of Phase Inversion Temperature (PIT) is based on the behaviour of poly-oxyethylene-type surfactants, which may not always be soluble at a specific temperature. When the temperature increases, these surfactants become lipophilic as the polymer chain undergoes dehydration (Fig 5). At lower temperatures, surfactant monolayers display a significant positive spontaneous curvature, resulting in an oil-swollen micellar solution phase.

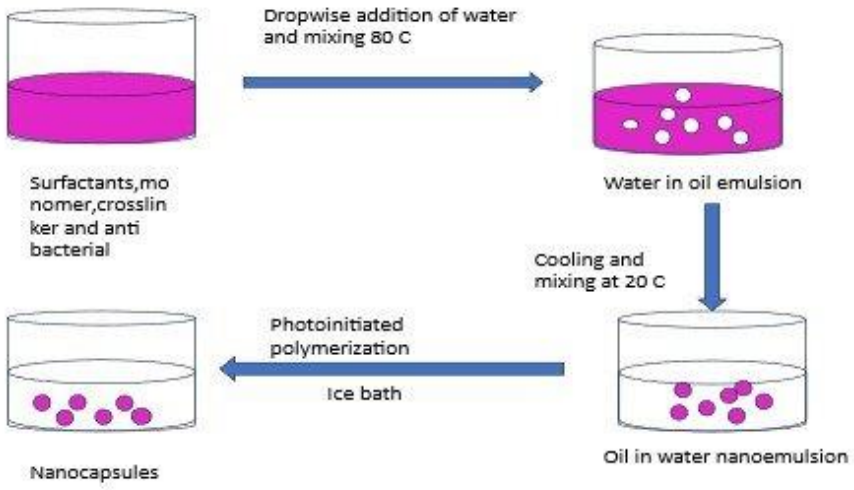

Figure No. 5. Phase inversion temperature (PIT)

CHARACTERIZATION OF NANOEMULSION

1. Drug content

UV visible spectroscopy approach can be used to measure the drug content in drug nanoemulsion formulation. Using a diluting solvent, prepare an aliquot containing 2 µg/ml of nanoemulsion formulation. The UV-VIS spectroscopic method can be used to measure the samples' maximum wavelength. The average was taken into consideration, and the results should be interpreted in triplicate [9].

2. **Determination of zeta potential**:
The measurement of zeta potential is conducted using the Malvern Zetasizer. This involves diluting the NE and determining the zeta potential value by assessing the electrophoretic mobility of the oil droplets. It is thought that a zeta potential of ±30 mV is adequate to guarantee the physical stability of the nanoemulsion. Đorđević *et al*. used the Malvern Zetasizer to obtain a zeta potential of around –50 mV for their risperidone nanoemulsion.[10]

.**3. Dynamic Light-Scattering measurements (Tanojo *et al.*,1997)**
Dynamic Light Scattering (DLS) is a technique used to measure the size of particles in a solution by analyzing the fluctuations in the intensity of scattered light caused by Brownian motion. In your scenario, a neon laser with a wavelength of 632 nm is used to perform DLS measurements at 90°.[11]

4. Polydispersity
Polydispersity is the ratio of the standard deviation to mean droplet size, so it indicates the uniformity of droplet size within the formulation. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation. Malvern Zeta sizer is based on dynamic light scattering and measures polydispersity. Using photon correlation spectroscopy, the average diameters and polydispersity index of the samples were determined. A He-Ne laser was used to do the tests at 25 °C.

5.Phase behaviour study:
The main objectives of this investigation are to characterize and optimize the ingredients involved, including the emulsifier, oil, and aqueous phases. This typically involves conducting studies to determine the phases of nanoemulsions and their dispersibility, particularly in formulations prepared using the Phase Inversion Temperature (PIT) method and self-nano emulsification methods.

6. Dye test :
When a water-soluble dye is introduced into an o/w nanoemulsion, the nanoemulsion uniformly adopts the color. In contrast, if the emulsion is of the w/o type and the dye is water-soluble, the color is only absorbed in the dispersed phase, resulting in non-uniform coloring of the emulsion. This distinction becomes immediately apparent upon microscopic examination of the emulsion**.[12]**

7. Dilutability Test :
While W/O nanoemulsions undergo phase inversion into O/W nanoemulsions, O/W nanoemulsions can be diluted with water.[13]

8. Conductance Measurement
Water is the external phase in O/W nanoemulsions, whereas water is the internal or dispersion phase in W/O nanoemulsions, which are not as powerfully conducting. Electrical conductivity tests are very helpful in identifying the type of continuous phase and identifying phase inversion occurrences. At low volume fractions, a significant increase in conductivity was seen in some W/O nanoemulsion systems; this behavior was taken as a sign of "percolative behavior," or the movement of ions between droplets before the creation of bi-continuous structures. Dielectric measurements are an effective way to examine the dynamic and structural characteristics of nanoemulsion systems.[13]

9. Viscosity:
Viscosity should be measured to ensure a better delivery of the formulation. It is measured by using Brookfield-type rotary viscometer.[13]

10. Phase Analysis:
Using a conductometer to measure electrical conductivity, one can ascertain the type of nanoemulsion that has formed the phase system (O/W or W/O) of the nanoemulsions.[13]

11. Interfacial Tension (Leong et al., 2009)
Measuring the interfacial tension allows for the study of the production and characteristics of nanoemulsion. Extremely low interfacial tension levels are associated with phase behavior, namely the presence of the middle phase or surfactant phase. Nanoemulsions with oil and water phases in balance. Ultra-low interfacial tension can be measured with a spinning-drop device. The measurement of a low-density phase drop's shape while it rotates in a cylindrical capillary filled with a high-density phase yields interfacial tensions. [14]

12. pH:
pH of the nanoemulsion is another crucial factor. The formulation's excipients determine the final preparation's pH and, consequently, the administration route. The formulation's zeta potential may be impacted by the pH shift, which may thus have an impact on the preparation's stability. With a digital pH meter, the formulations' pH was determined. The average of the three sets of results was considered.[15]

13. Stability Studies

The goal of this study is to determine how stable the drug candidate will be in various drug compounds as well as environmental conditions including humidity, temperature, and light. A stability analysis of the nanoemulsion is conducted, as per the recommendations of the ICH (International Conference on Harmonization), following at least 730 days of storage of the preparation in a freeze-dried or dispersed condition. Low temperature (25°F/60°RH), freeze (−20°F), and refrigeration (5°F) temperature storage conditions are used for these investigations. Samples of the important section of the nanoemulsion are taken at pre-arranged intervals and stored in tightly sealed glass vials. Among other features, particle size, polydispersity index, entrapment effectiveness, and drug release profiles were also looked at.[8]

14. Refractive Index (Aubrun et al., 2004)

The purpose of this study is to determine how stable the drug candidate is in response to various drug substances, that is, the ratio of the phase speed (vp) of a wave in a medium to its speed (c), such as sound or light, in a reference medium, is known as the refractive index (n) of the media. n=c/vp was calculated at 25±0.5°C using an Abbes-type refractometer (Nirmal International)[16].

15. *In Vitro* Skin Permeation Studies:

Keshary Chien diffusion cells were used for *in vitro* skin penetration studies. It was carried out on male rats weighing 250±10 gm, whose abdomen skins were acquired together with 12 diffusion cells and a recirculating water bath. The skins were positioned in between the vertical diffusion cell's donor and recipient chambers. Twenty percent ethanol was added to fresh water that was poured into the receiver chambers. The solution within the receiver chambers was continually agitated at 300 rpm while the chambers were maintained at 37 °C. The donor chamber was filled with the compositions. 0.5 ml of the solution in the receiver chamber was taken out for analysis at 2, 4, 6, and 8 hours, and it was quickly replaced with an equivalent volume of brand-new solution. Every sample was run through three times.

To determine the overall amount of drugs dispersed at each period, cumulative adjustments were used. Plotting the total drug concentrations through the rat skins as a function of time was done. The slope of the linear part of the cumulative amount permeated through the rat skins per unit area vs time plot was used to calculate the drug's steady-state permeat7ion rates through rat skins[17].

Marketed products:

Nanoemulsion formulations containing various drugs are available in the market as shown in table no 3.

Table No.3: Marketed product of nanoemulsion

Drugs	Brand name	Indication
Propofol	Diprivan	Anaesthetic
Dexamethasone	Limethason	Steroid
Palmitate alprostadil	Liple	Vasodilator, platelet inhibitor
Etomidate	Etomidate-lipuro	Anaesthetic
Ritonavir	Norvir	Antiretroviral
Flurbiprofen	Ropion	NSAID

APPLICATIONS OF NANOEMULSIONS:

Nanoemulsion formulations have been reported for a wide range of drugs for solubility, permeability, and bioavailability enhancement with different routes *viz.* oral, ocular, transdermal, topical, intranasal as shown in table no 4. and parenteral in table no 5.

1. Oral delivery

Oral drug delivery is the most practical, straightforward, and economical method of administering medications noninvasively. As a result, drug delivery systems built on this premise today rule the pharmaceutical industry. It's also the best way to hit therapy goals because of higher patient compliance. The use of nanoemulsions in elderly, pediatric, and potentially traumatized epileptic patients when patient compliance is a significant barrier Nano emulsions loaded with various drugs have been reported for oral route as depicted in table no 4.

Katrin Zoller *et al.*,(2023) created and evaluated low molecular weight heparin (LMWH) *in vivo* utilizing several nanoemulsion forms. Mostly indigestible substances and various PEGylated, zwitterionic, or polyglycerol-type surfactants were used to make nanoemulsions (NE). By employing several cationic surfactants to create hydrophobic ion pairs, LMWH was added to the oily droplets. Dimensions, zeta potential, stability against pancreatin, haemolytic and toxic characteristics, and stability against loaded and unloaded NE were assessed. Finally, an *in vivo* investigation was carried out regarding the oral administration of LMWH. All formulations had droplet sizes less than 150 nm with a PDI of less than 0.4. The combination of LMWH and di-decyl dimethylammonium bromide (HIP) produced the highest logK1-butanol/water ratio. This complex was added to the polyglycerol-containing NE and PEGylated surfactants up to 10% (m/m) in zwitterionic NE and 5% (m/v) in other concentrations. The degree of digestion of NE-containing polyglycerol-surfactants was higher than that of NE-having PEGylated surfactants. The zwitterionic NE without glycerides did not show any lipolysis, whereas the NE with a considerable glyceride concentration broke down fast. When NE was compared to zwitterionic and PEGylated surfactants, polyglycerol surfactants showed reduced toxicity and haemolysis. Formulations containing HIP had a higher potential for toxicity. Oral bioavailability of LMWH was up to 2.6% higher with non-digestible NE while conducting *in vivo* investigations. These findings suggest that non-digestible nanoemulsions are a more effective way than biodegradable formulations to increase the oral bioavailability of LMWH.[18]

Table No 4. Bioavailability Enhancement with Nanoemulsion Formulations

Drugs	**Therapeutic Category**	**Remarks on Bioavailability Enhancement**	**Reference**
Oral route			
Fisetin	Antitumor	Higher compared with free fisetin	Ragelle *et al.,* (2012) [19]
Glyburide	Antidiabetic	1.5-fold increase of AUC compared with commercial tablet	Liu *et al.* (2014)[20]
Mebudipine	Antihypertensive	Bioavailibility is 2.6-, 2.0-, and 1.9-fold higher, respectively, compared with suspension, ethyl oleate solution, and micellar solution.	Khani *et al.* (2016)[21]
Celecoxib	anti-inflammatory	to improve the solubility	Maru S *et al*,2023. [22]
Isoformononetin	Anti-cancer	Oral bioavailability	Sultana N *et al*,2024 .[23]
Carvacrol	antioxidant, antimicrobial and anti-inflammatory activities.	To improve the bioavailability	De Souza RL *et al*,2023 [24]
Cariprazine	antipsychotics	improvement of the bioavailability	Hamed HE et al,*2023* .[25]
OCULAR			
Restasis	Dry eyes treatment	To improve bioavailability enhancement	Dukovski *et al*., 2023.
Brimonidine	glaucoma	To improve bioavailability enhancement	Prajapati B et al., 2024
Prednisolone	uveitis management	To improve bioavailability enhancement	Attia MA *et al.,* 2024

Curcumin	anti-inflammatory	To improve bioavailability enhancement	Jahromy MH *et al*.,2024
Betaxolol hydrochloride	Glaucoma	To improve permeation	Sakr et al,2023
Fluconazole	Anti fungal	To evaluate the permeability of nanoemuldion preparation	Gawin-Mikołajewicz A *et al.,* 2023
Besifloxacin	Antibiotic	To improve permeation	Kassaee SN *et al*., 2023
TRANSDERMAL			
Curcumin	Anti inf lammatory	To Improve permeation	Rachmawati H *et al*.,2015
Celecoxib	Anti- inflammatory	To improve permeationgranisetron hydrochlioride	Baboota S *et al*, 2007
Granisetron hydrochlioride	Nausea and vomiting	To improve permeability	Zheng WW *et al*,2010
Glimepiride	Anti diabetic	To potentiate the systemic bioavailability of gm	Abdallah MH *et al*,2013
Acyclovir	Anti-viral	To improve permeability	Telange TS *et al*,2023
TOPICAL			
Luliconazole	Anti fungal	Improve permeation	Kmkm AM *et al*,23
Mupirocin		To enhance transdermal permeation	Alhasso B *et al*,23.
Piroxicam	Anti inflammatory arthritic disease	To enhance permeability	Gaber DA *et al*,23
Azelaic acid and vitamin E oil	psoriasis	Improve permeation	Rai V K *et al*,2023
NASAL			
Temozolomide	glioblastoma	Increasing brain bioavailability	Michels LR *et al*,2023
Olanzapine	Schizophrenia	Bioavailability enhancement	Ali ZH *et al*,2023
Dolutegravir	NeuroAIDS	Bioavailability enhancement	Nair AB *et al*,2023
Diazepam	epileptic	Enhance bioavailability	Younis YK *et al*,2023
Propranolol	Migraine	To enhance bioavailability	Abla KK *et al*,2023
Amphotericin B	Cryptococcal meningitis	To enhance bioavailability	Mualim E *et al,*2024

2.Ocular delivery:

Majority of ocular medicines have been applied topically to the lower conjunctival sac as eye drops made of straightforward aqueous solutions (Tatham ***et al.***, 2013). The numerous benefits of nanoemulsions, including their strong drug penetration into the aqueous humor and deeper layers of the ocular structure, as well as their prolonged action, make them effective drug delivery vehicles for use in the eye (Ammar *et al.*, 2009; Daull *et al*., 2014).

It has been demonstrated that cationic nanoemulsions with bio-adhesive qualities are more effective in delivering the right amounts of bioactive compounds for eye drops than the methods that are currently on the market to the visual organs. The electrostatic interaction that extends the residence period of the tiny oil droplets on the ocular surface is the mechanism responsible for these nanoemulsions' bio-adhesive properties.

Dexamethasone-loaded nanoemulsions were developed by Jadhav *et al.,* (2023) using the Quality by Design (QbD) methodology to treat inflammatory disorders of the anterior portion of the eye. The commercially available formulations have several problems, such as short drug residence times that necessitate frequent dosing, which reduces their effectiveness: Seven independent variables were screened using a Plackett-Burman Design (PBD), including oil concentration, surfactant concentration, polymer concentration, homogenization speed and time, microfluidization pressure and cycles, and their impact on critical quality attributes (CQAs) like viscosity, globule size, and zeta potential. Additionally, optimization was performed using the BoxBehnken Design (BBD), and design space was produced to get the DEX NE that is optimal. The experimental results show a globule size of 181 ± 90 nm, a viscosity of 19.99 cp, and a zeta potential of -21.03 ± 1.68 mV. Additionally, a prolonged and constant release of the drug was shown for up to 48 hours in the drug release testing using simulated tear fluid. DEX NE's cytotoxicity test showed good cell viability.[26]

3.Transdermal delivery:

For several therapeutic diseases, systemic medication distribution through the skin is very practical (Pattnaik *et al.*, 2011, 2015d; Swain *et al.*, 2010, 2011). Transdermal delivery systems are particularly appealing because of the benefit of steady-state regulated drug delivery with the possibility of self-administration, which may not be the case with the parenteral route (Swain *et al.*, 2009). The patient can stop receiving medication at any moment by simply taking off the transdermal patch.

A curcumin nanoemulsion is created by Heni s *et al.,* (2015)for transdermal administration. The stabilization and permeability of curcumin should be enhanced by encapsulating it in a nanoglobule. The self-nanoemulsification method was used to create a nanoemulsion with an oil phase consisting of polyethylene glycol 400, glyceryl monooleate, and Cremophor RH40. Furthermore, the nanoemulsion's physical performance in Viscolam AT 100P gel was investigated. The in vitro permeation of curcumin was investigated using a modified vertical diffusion cell and shed Python reticulatus snake skin. The loading capacity of a stable, spontaneously generated nanoemulsion is 350 mg curcumin/10 g of oil phase. The zeta, polydispersity index, and mean droplet diameter The optimum nanoemulsion had a potential of 85.0 ± 1.5 nm, 0.18 ± 0.0, and 5.9 ± 0.3 mV, in that order. Furthermore, curcumin's release kinetics shifted from zero order to a Higuchi release profile as a result of nanoemulsification, which also markedly increased the penetration flux of curcumin from the hydrophilic matrix gel. All things considered, the created nanoemulsion technology enhanced curcumin's permeability while shielding it from chemical deterioration.

Marwa H. Abdallah *et al.,*. creating and validating a nanoemulsion (NE) system for transdermal delivery of the oral hypoglycemic medication glimepiride (GM). The NEs were made with tween 80/Transcutol P as the surfactant/co-surfactant mixture (Smix) and peppermint/bergamot oils as the oil phase. The results of characterization studies showed that NE droplets had a spherical shape, with an average size of about 80 nm and a zeta potential of -11.8 mV, indicating good electrokinetic stability. Comparing the NE formulation to the plain medication *in vitro* release experiments, the NE formulation showed improved drug release. In comparison to conventional drug gel, GM-loaded nanoemulgel demonstrated a seven-fold increase in drug transdermal flux. Furthermore, there were no indications of inflammation or irritation on the applied skin from the GM-loaded nanoemulgel formulation, indicating its safety. Nanoemulgel formulation may increase the systemic bioavailability of GM by ten times, as seen by a ten-fold increase in the bioavailability ratio relative to the control gel. All things considered, oral medication for the treatment of diabetes may not be as effective as transdermal NE-based GM gel.

4. Topical drug delivery:

Treatment for skin cancer can be greatly enhanced by topical nanoemulsions. Increased skin drug delivery patterns and biocompatibility are made possible by nanoemulsions. Nanoemulsions provide greater bioavailability and therapeutic efficacy. Promising topical drug delivery methods for the treatment of skin cancer include nanoemulsions.

Donthi MR *et al,*2023 developed the topical nanoemugel. The objective of the current study was to minimize systemic adverse effects associated with the therapy of rheumatoid arthritis (RA) by creating a topical emulgel containing dasatinib (DTB). Using a central composite design (CCD), the DTB-loaded nanoemulgel was optimized through the use of the quality by design (QbD) methodology. The homogenization approach was used to lower the particle size (PS) after the hot emulsification method was used to prepare the emulgel. The results showed that the PS and % entrapment efficiency (% EE) were 95.11 ± 0.16% and 172.53 ± 3.33 nm (0.160 ± 0.014 PDI), respectively. The sustained release (SR) of the nano-emulsion (CF018 emulsion) in vitro

drug release profile lasted for up to 24 hours. An in vitro cell line study's MTT assay results showed that emulgel had a high degree of internalization whereas formulation excipients had no effect. Additionally, emulgel therapy effectively decreased the generation of TNF-α in RAW 264.7 cells stimulated by LPS. FESEM pictures of the improved nanoemulgel (CF018 emulgel) formulation showed a spherical shape. Comparing ex vivo skin penetration to the free drug-loaded gel (FDG), a considerable increase was observed. The optimized CF018 emulgel is safe and non-irritating, according to in vivo research. The CF018 emulgel decreased the proportion of paw swelling in the FCA-induced arthritis model when compared to the adjuvant-induced arthritis (AIA) control group. After conducting clinical trials in the near future, the developed product may prove to be a practical substitute therapy for RA.

Abdhesh *et al.(*2020) developed and assessed an aceclofenac nanoemulsion-based nanoemugel to increase its bioavailability, stability, permeability, and effectiveness in the treatment of arthritis.Oleic acid was selected as the oil phase, Tween 20 and ethanol were employed as surfactant and cosurfactant, respectively, in the preparation of nanoemulsions by the aqueous titration method. To determine the nanoemulsion zone, pseudo ternary phase diagrams were built. Additional tailored NE was added to various Carbopol-940 concentrations to create a gel that would make the drug application process. Particle size, viscosity, rheological behavior, and thermodynamic stability experiments were performed on drug-loaded NE and NEG. Findings: When comparing the optimized formulation to the traditional gel formulation, it shown a greater permeability rate both *in vitro* and *in vivo*, supporting the nanoemulsion gel's potential as a transdermal aceclofenac delivery vehicle. Compared to the standard gel, which released 68.2% release of the drug after approximately 9 hours, the improved formulation demonstrated a greater drug release of 90.2%. According to the study, aceclofenac administered transdermally had far higher bioavailability when it was in a nanoemulsion

5. Parenteral Delivery:

Parenteral administration is thought to be one of the most popular and successful ways for medications with low bioavailability and narrow therapeutic index (Gassmann *et al.*, 1994; Kalepu and Nekkanti, 2015). But in the case of medications with little water solubility, parenteral a significant obstacle in the field of drug delivery is administration. According to Cheng *et al.* (2016) and Đorđevic *et al.* (2015), the stability of nanoemulsions used for parenteral distribution is primarily determined by their compositions, preparation methods, and storage conditions.

The phospholipids that are most frequently utilized in the formulation of parenteral delivery systems come from semisynthetic materials like dioleoyl phosphatidylethanolamine (DOPE) and distearoylphosphatidylcholine (DSPC) or from natural sources like lecithin's.

Table.No. 5 Bioavailability enhancement of parenteral Nanoemulsions

Drug	**Therapeutic activity**	**Remarks on Bioavailability Enhancement**	**References**
Carbamazepine	Anticonvulsant	To enhance bioavailability	Kelmann RG *et al,*.2007
Thalidomide	aphthous ulcers, sepsis, Behcet's disease, and some chronic degenerative diseases	To enhance solubility	Araújo FA *et al,*.2011
Primaquine	Anti-malarial	To enhance bioavailability	Singh KK *et al* ,.2008
fisetin	Anti-tumour	To enhance bioavailability	Ragelle H *et al*,.2012
Phenytoin	Epilepsy	To enhance bioavailability	Yang MY *et al,*.2023

6.Intranasal drug delivery:

Another dependable method for administering some medications is intranasal drug delivery. In fact, the nasal mucosa has shown to be a therapeutically effective route for systemic drug delivery, and it also seems to be a good means to get around barriers that prevent medications from entering the target site directly. Since it produces better systemic bioavailability possibly by avoiding the drug's gastrointestinal metabolism this method has been accepted in the Ayurvedic system of Indian medicine since ancient times. More recently, it has frequently been chosen over oral drug administration (Rahisuddin *et al*., 2011). Additionally, the intranasal method is well tolerated, painless, and non-invasive. Targeting the brain with medications presents several issues, particularly with hydrophilic ones and those with a high molecular weight (Marianecci *et al.*, 2015; Bahadur and Pathak, 2012). Permeability, residence time, and metabolism in the nasal cavity are all impacted by drug distribution, which is frequently influenced by the delivery method, formulation, and administration strategy.

CONCLUSION

In pharmaceutical systems, nanoemulsions are commonly employed. Their use of nanoemulsion formulation has many benefits, including the delivery of biological, medicinal, and diagnostic agents. The primary use of nanoemulsion is to cover up the unpleasant flavour of oily liquids. The medications, which are vulnerable to oxidation and hydrolysis, may also be protected by the nanoemulsion. These days, medicinal medicines, light sensitizers, and anticancer medications are delivered specifically to specific areas of the body via nanoemulsions. They are easily targetable to the tumor location because of their submicron size. Moreover, nanoemulsion can extend the duration of a medication's activity. All nanoemulsion formulations can be regarded as safe, efficacious, and having higher bioavailability overall. It is anticipated that more studies and developments pertaining to nanoemulsion will be conducted in the future. They can be applicable for almost all routes of drug delivery systems.

CONFLICT OF INTREST

There is no conflict in publishing of this manuscript

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