IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

NANOEMULSION: A NOVEL APPROACH

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ABSTRACT: The nanoemulsion is dispersed nano-system with droplet sizes ranging from sub-micron to micron. In these thermodynamically stable isotropic systems, a single phase formed by mixing two immiscible liquids by surfactants and co-surfactants. Nanoemulsions are being studied as drug carriers for improving active pharmaceutical ingredient delivery. Nanoemulsion having droplet sizes ranging from 20 to 200 nm, received considerable attention in a variety of fields since last few years. They have been researched thoroughly as the systems of drug delivery. The present review aims to present a basic understanding of nanoemulsion formulation, preparation techniques, characterization, evaluation, and variety of applications.

Keywords: Nanoemulsions, Lipophilic, Droplet size, entrapment efficiency

I. INTRODUCTION

Nanoemulsions are oil-water dispersions that are thermodynamically stable and are held together by an interfacial layer of molecules from cosurfactants and surfactants with droplet sizes less than 100nm. The stability and clarity of a nanoemulsion, also called a multiphase colloidal dispersion, set it apart. The dispersed phase has a very low/water oil interfacial tension and is composed of tiny droplets with diameters ranging from 5-200nm. Because the size of the individual droplets in nanoemulsions is lesser than 25% of visible light wavelength, they are transparent. Because the size of the individual droplets in nanoemulsions is lesser than 25% of visible light wavelength, they are transparent. Nano-emulsions may sometimes and swiftly develop on their own with small amount of energy. A cosurfactant or cosolvent is often employed together with the surfactant, water and oil phase.[1,26,28]

Nanoemulsions are grouped into two categories as per the size of the droplet: translucent or transparent (50-200nm) and milky (up to 500nm). A nanoemulsion is advantageous to a macroemulsion due to its modified release. larger surface area, and properties of drug-carrier, improved occlusive ness, high stability, formation of films on eyelids, skin feel and pleasing aesthetic character.[2,31]

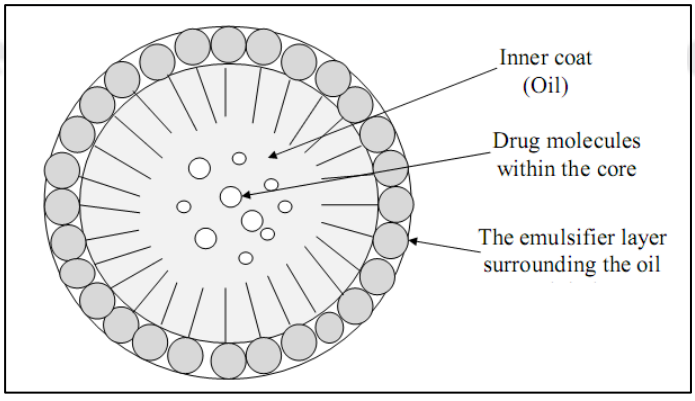


Fig 1. Structure of Nanoemulsion

Each type of nanoemulsion is used to produce polymer latex particles, nano-porous polymeric solids, and other materials. Furthermore, the formation of drugs used for oral delivery uses nanoemulsions that are pharmaceutically acceptable. Ultra-fine emulsions, sub-micron emulsions, mini-emulsions are additional names for nanoemulsions.[3]

Primary application for nanoemulsions is its mini-emulsion polymerization method, which involves using nanoemulsion droplets as nanoreactors to prepare nanoparticles in disperse phase using polymerizable monomers. Another exciting application in active growth is that of using formulations of nanoemulsions, especially for controlled drugs delivery and targeting.[4]

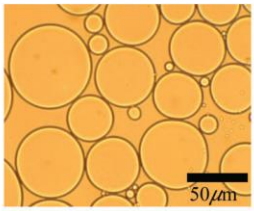
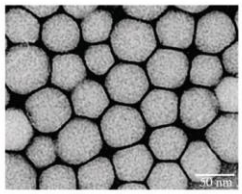
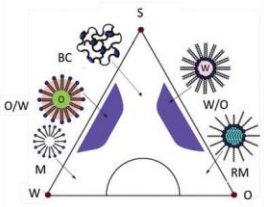
	macroemulsions	nanoemulsions	microemulsions
			
size	1-100 μm	20-500 nm	10-100 nm
shape	spherical	spherical	spherical, lamellar
stability	thermodynamically unstable, weakly kinetically stable	thermodynamically unstable, kinetically stable	thermodynamically stable
method of preparation	high & low energy methods	high & low energy methods	low energy method
polydispersity	often high (>40%)	typically low (<10-20%)	typically low (<10%)

Fig 2. Comparison of Macroemulsions, Nanoemulsions (Or Miniemulsions) And Microemulsions.[5]

II. TYPES

Emulsions are classified using both morphological and compositional characteristics. Depending on the composition, three types are occurring:

- Bi-continuous Nanoemulsion: Water and oil micro-domains in a system are inter-dispersed.
- Oil-in-Water (O/W) nanoemulsions: oil droplets in an aqueous continuous phase;
- Water-in-Oil (W/O) nanoemulsions: water droplets immersed throughout in complete oil phase;

All above types use surfactants or combinations of surfactants and/or cosurfactants to stabilise the interface.[6]

based on the type of surfactant used, O/W nanoemulsions are categorised further in three:

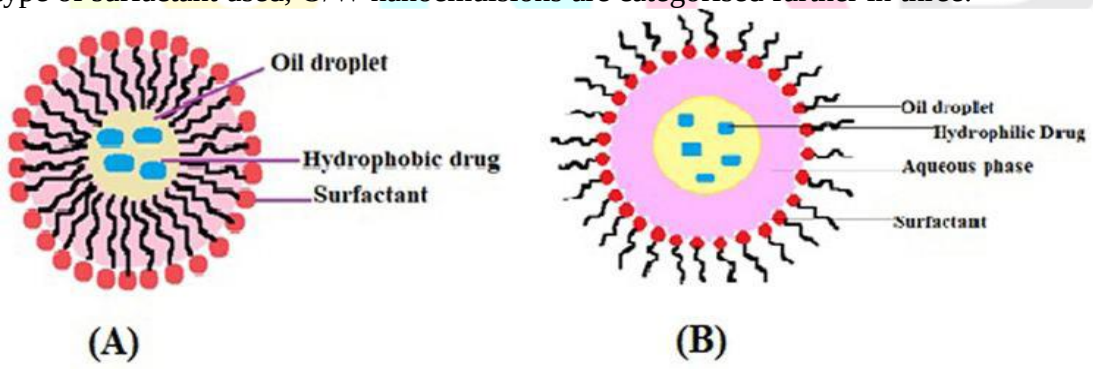


Fig 3. (A) O/W; (B) W/O nano-emulsion[7]

- Neutral O/W nanoemulsions, which use a neutral surfactant.
- Cationic O/W nanoemulsions with cationic surfactants.
- Anionic O/W nanoemulsions made with anionic surfactants[7]

Nanoemulsion Advantages:[8,9,10]

1.Nanoemulsions can deliver drugs that are both hydrophilic and lipophilic.

2.Kinetically and thermodynamically stable, which prevents Aggregation, Flocculation, Coalescence, and Creaming.

3.They are not toxic or irritating.

4. It is administered via a variety of routes, including oral, topical, parenteral, and transdermal.

5.Due to encapsulation in oil droplets, nanoemulsions are protected from oxidation and hydrolysis. It also provides taste masking.

6.They are safe for human and veterinary use since do not cause cell damage in either humans or animals.

7.Improves drug permeation through the skin.

8.Improved effectiveness with reduced total dosage and adverse effects is the goal of several innovative delivery strategies.

9.Drug bioavailability is increased because to the nanoscale droplets' larger surface area, which increases the decreases variability and rate of absorption.

10. It is available in Foams, Creams, Liquids, and Sprays.

11. It could be used as a substitute for vesicles and liposomes.

12. It improves the uptake of oil-soluble nutrients in the technology of cell-culture.

13. Less energy is required.

Nanoemulsion Disadvantages:[8,9]

1.Large concentration of co-surfactant or surfactant required for stabilization.

2.Extremely high-melting-point compounds are difficult to dissolve.

3.Temperature and pH have an effect on its stability.

4.The Oswald ripening effect can lead to instability.

5.Expensive process as a result of droplet-size reduction

III. COMPONENTS OF NANOEMULSION

(a) Oil:

Water is the most significant vehicle and oil comes second, as it has an ability of solubilizing the molecules of lipophilic drugs and also helps in improving the absorption by lipid layer present in the body. Oil is very useful for lipophilic active delivery of drug due to its unique ability to penetrate cell walls. The oil phase influences the swelling of the tail group region of surfactant. In comparison to long chain alkanes, short chain alkanes have better penetration (table 1).[7]

(b) Surfactant:

To aid in the dispersion of all components, the surfactant can help in decreasing the interfacial tension to almost zero. Surfactants with HLB values of 3-6 are useful for creating W/O nanoemulsions, but surfactants with higher HLB values of 8-18 are needed to create O/W nanoemulsions. Surfactants with HLB values greater than 20 work as cosurfactants to generate microemulsions by bringing surfactant concentrations within a suitable range (Table 1).[7]

(c) Co-surfactant:

For reducing interfacial tension between water and oil to the level which enables spontaneously forming nanoemulsion, higher concentration single-chain surfactants are needed. Because of the presence of fluidizing groups such as unsaturated bonds, cosurfactant increases the fluidity of the interface, demolishing the gel structure or liquid crystalline and altering the HLB value in a manner that spontaneous nanoemulsion formation occurs (Table 1). [7]

(d) Aqueous phase

Nature of aqueous phase like the pH value, the electrolytes, and the ionic content, changes the nanoemulsion stability and droplet size. In case of nanoemulsions, the spontaneous nano-emulsification is estimated using plain water; phosphate buffered saline, pH-6.8 simulated intestinal fluid, pH-1.2 simulated gastric fluid, and Ringer's solution could be used as the aqueous phase. When a pH-dependent solubility drug is put into a system, pH of aqueous phase has a substantial effect on phase behaviour of nanoemulsions.[6]

(e) Co-solvents

Used for improving the dissolution of either large amounts of drugs or hydrophilic surfactant in lipid base through co-solvency. Organic solvents like Propylene Glycol (PG), Polyethylene Glycol (PEG), ethanol, glycerol, are suitable organic solvents for oral delivery. They increase the hydrophobic environment by lowering the water's dielectric constant. Drug precipitation is caused by alcohols and other flammable co-solvents evaporation into soft gelatin or hard gelatin capsule shells. As a result, formulations without alcohol have been developed.[12]

Table 1. Formulation Ingredients [11]

Components	Examples
Oils	Castor oil, Corn oil, Coconut oil, Evening primrose oil, linseed oil, Mineral oil, olive oil, peanut oil
Emulgent	Natural lecithins from plant or animal source, phospholipids, castor oil. Derivatives, polysorbates, sterylamine
Surfactant	Polysorbate20, Polysorbate80, Polyoxy-60, castor oil, Sorbitan mono oleate, PEG300, Caprylic glyceride
Co- Surfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer
Tonicity modifiers	Glycerol, Sorbitol and xylitol
Additives	Lower alcohol (ethanol), propylene glycol, 1, 3-butylenes glycol, sugars such as butylenes glycol, sugars such as glucose, sucrose, fructose, and maltose
Antioxidants	Ascorbic acid and tocopherol

IV. TECHNIQUES OF PREPARATION OF NANOEMULSION:

Since nanoemulsions are non-equilibrium systems of structured liquids, they need a lot of energy, surfactants, or a combination of both. Therefore, low or high energy formulation techniques may be employed.

(1) High Energy Methods:

High kinetic energy nanoemulsions are produced when strong disruptive forces are utilised to split apart larger droplets into nano-sized droplets. Mechanical tools including ultra-sonicators, microfluidizers, and high-pressure homogenizers are employed to produce disruptive forces. [13]

(a) High Pressure Homogenization

A high-pressure piston/homogenizer is used in this technique for creating nanoemulsions with up to 1nm small sized particles. It is possible to disperse two liquids (aqueous and oily phase) by applying high pressure (500–5000 psi) to a small inlet orifice, causing the combination to undergo hydraulic shear and strong turbulence, and producing very minute emulsion particles. A monomolecular coating of phospholipids surrounds the liquid, lipophilic core of the produced particles, keeping it isolated from its surrounding aqueous phase. The primary downsides of this approach are its high energy need and processing-induced increase in emulsion temperature.[11]

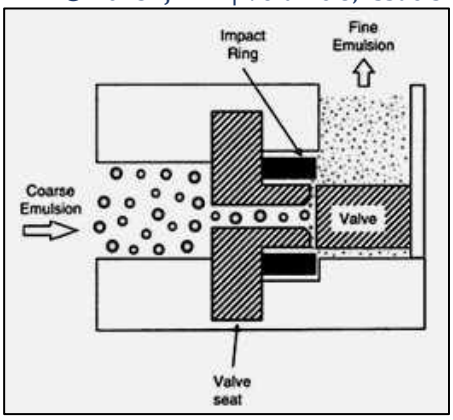


Fig 4. High Pressure Homogenization [14]

(b) Microfluidization

Microfludizer is a patented mixing mechanism. Using a high-pressure (from 500 to 20000psi) positive displacement pump, the product is pushed into an interaction chamber, that is made of microscopic channels known as the "microchannels". In an impingement region, where the product passes via microchannels to create extremely small submicron particles. A coarse emulsion is created by combining and homogenising the two solutions (the oily and aqueous phases) in an inline homogenizer. A microfluidizer is used to further convert the coarse emulsion into a stable nanoemulsion.[15]

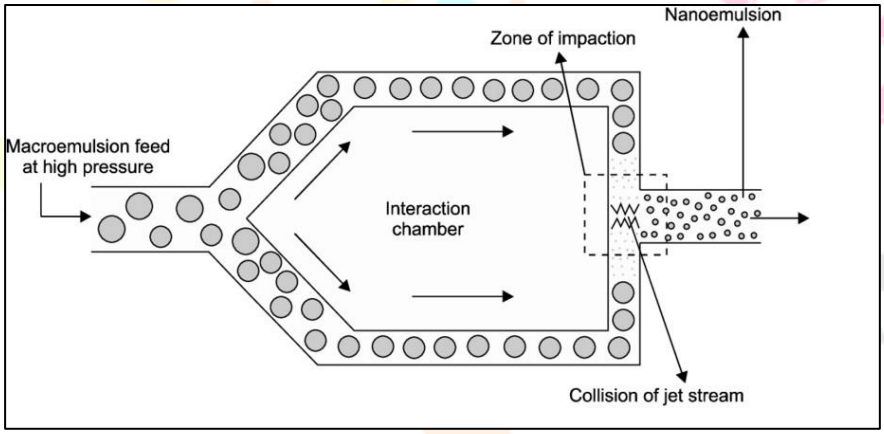


Fig 5. Microfluidization [13]

(c) Ultrasonification

Ultrasonic emulsification is highly effective at reducing droplet size. Sonotrodes, often referred to as sonicator probes, provide the energy for ultrasonic emulsification. It features a quartz piezoelectric crystal that responds to alternating electric energy by expanding and contracting. Mechanical vibration and cavitation are brought about when the sonicator's tip comes into contact with the liquid. The creation and dissolution of liquid-vapour cavities is known as cavitation. As a result, ultrasonic are used for creating emulsion directly; primarily used in labs to manufacture emulsion droplets as thin as 0.2 micrometres.[10,27]

(2) Low Energy Methods:

Low-energy emulsification techniques utilise the system's intrinsic chemical energy and just mild agitation to create nanoemulsions, making them more energy-efficient. Such methods are as follows:[13]

(a) Phase Inversion Method

This approach uses chemical energy from phase transitions brought on by emulsification to achieve fine dispersion. The requires transition of phase is done by keeping the temperature constant and changing the composition or vice-versa. PIT: "Phase Inversion Temperature" was based on an idea that the solubility of surfactants of the polyoxymethylene type changes with variations in temperature. The dehydration of the polymer chain results in this surfactant becoming lipid soluble as the temperature rises. A high positive spontaneous curvature is exhibited by surfactant monolayers on low temperatures, resulting in the formation of an oil-swollen micellar solution phase. [8]

(b) Spontaneous Emulsification[11]

There are three primary steps.
(i) Using a hydrophilic surfactant and a water-miscible solvent to create a homogenous organic solution of a lipophilic surfactant and oil.
(ii) Organic phase was injected into aqueous phase and magnetic stirring was used for producing the O/W emulsion.
(iii) Evaporation under reduced pressure to remove a water-miscible solvent.

Factors to consider when creating a nanoemulsion:[16]

(i) Choosing the right surfactant is essential for obtaining ultralow interfacial tension, which is a necessity when making nanoemulsion.
(ii) The microdroplets must be stabilised and the surfactant concentration must be high enough to form a nanoemulsion.
(iii) Surfactant should be adaptable or fluid enough for encouraging the development of nanoemulsions.

V. CHARACTERIZATION OF NANOEMULSION:[33]

(a) Droplet size analysis

Using a diffusion approach and a light-scattering particle size analyser Coulter LS-230, the droplet size distribution, a crucial physicochemical characteristic of a nano-emulsion, was determined. It determines particle size distribution using laser light diffusion. In polarisation intensity differential scattering, polarising filters, an incandescent light source, seven photodiode detectors and PIDS sample cell are utilised. A measuring chamber is filled with 0.5 ml of emulsion to determine the size distribution of the droplets (125ml water). The volume distribution is used to depict the outcomes.[17,39]

(b) Viscosity Determination

nanoemulsion system requires optimal viscosity. The viscosity of a nanoemulsion was measured at different temperatures and shear rates using a rotational viscometer of the Brookfield type.[18] A thermobath must be used to maintain the temperature of the instrument's sample room at 37,2°C. These samples for measurement must be submerged in it prior to testing.[4]

(c) Dilution test

When a nanoemulsion is diluted with oil or water, this kind may be observed. The hypothesis supporting the test is that increasing the amount of continuous phase may improve a nanoemulsion's stability. A W/O nano-emulsion may be diluted with oil as opposed to an O/W nanoemulsion, which can only be done using water.[10]

(d) Dye Solubilization

Oil-soluble dyes are those that is soluble in O/W globule oil phase and dispersible in W/O globule. The water-soluble dye is soluble in W/O globule aqueous phase but dispersible in O/W globule.[11]

(e) pH and Osmolarity Measurements

With a pH metre, the apparent pH of nanoemulsion was calculated and the osmolarity of the nanoemulsion was determined using a micro-osmometer based on the freezing point method.[19,30]

(f) Refractive Index

To determine the refractive index of nanoemulsions, an Abbes type refractometer is used.[20] The refractive index of nanoemulsion's medium and transparency allows light to travel through them. The ratio of the wave speed (c) in reference medium to wave speed (*vp*) in the media is known as the R.I. (n) of the medium. $n = c / vp$.[19]

(g) Conductance Measurement

The conductometer measures the conductance of a nanoemulsion. In this test, an emulsion is dipped between two electrodes that are connected to an electric source and a lamp. Water conducts current when emulsion is of the o/w type, and lamp will light up as a result of the current flowing between the electrodes. A lamp will not always glow when emulsion is without oil because current cannot flow through the exterior phase without oil. [10]

(h) Percentage Transmittance

A UV-visible spectrophotometer is used for determining the percentage transmittance of the prepared nanoemulsion. If the formulation has close to 100% or the highest percentage of transmittance, it is transparent

and clear. For this, a 1ml nanoemulsion is diluted 100 times with a specific solvent and then tested at max with the solvent as a blank. [7,40]

(i) Dynamic Light-Scattering measurements

To produce DLS measurements on 90 degrees, a neon laser with a wavelength of 632 nm is employed in a dynamic light scattering spectrophotometer. Data processing is done on the instrument's inbuilt computer.[9]

(j) Morphology of nanoemulsion

The morphology of a nanoemulsion is determined using "Transmission Electron Microscopy" (TEM). Using TEM, high-resolution images of the dispersion phase are produced.[15] The size and structure of the nanoemulsion droplets were revealed with a combination of diffraction modes and bright field imaging at increasing magnification. After drying, a nanoemulsion drop was applied directly to the grid of holes in the film.[21]

(k) Polydispersity Index and Zeta Potential Analysis

The polydispersity index measures how uniformly sized droplets are throughout a formulation. The formulation's droplet size uniformity will decrease as polydispersity increases. The standard deviation to mean droplet size is calculated using this ratio.[6]

Nanoemulsions are evaluated for their surface charge characteristics and long-term physical stability using their zeta potential. ZetaPALS is the name of the device used to measure the surface charge.[13]

(l) Drug Content

With the aid of a spectrophotometer or HPLC, a pre-weighed nanoemulsion is extracted by dissolving it in a solvent, and the extract is then contrasted with a standard drug solution. Using a C18 column and a reverse phase HPLC procedure, the drug content was identified.[10]

(m) Entrapment efficiency

A weighted portion of the formulation is dispersed using ultrasonication in an organic solvent to determine how much drug is entrapped in it. After that, the medication is removed into the proper buffer. By spectrophotometrically analysing the extract at the maximal concentration of drug after adequate dilutions against a suitable blank, the drug content is measured. Drug LE = Drug content in the obtained drug(mg)/total weight of the product(mg)*100; Drug EE= Drug content in the obtained drug(mg)/total amount of drug(mg)*100 are used for determining the drug's LE and EE (Loading Efficiency, and Entrapment Efficiency resp.) To ascertain the amount of drugs present, reverse-phase HPLC: "High-Performance Liquid Chromatography" may also be used. [19]

(n) In Vitro Skin Permeation Studies

Studies on *in-vitro* skin permeation employed the Keshary Chien-diffusion cell. It was carried out using 12 diffusion cells and a recirculating water bath using 250-10g male rat abdomen skins. Skins were inserted into receiver and donor chambers of vertical diffusion cells. Fresh water containing 20% ethanol was used to fill the receiver chambers. The solution was constantly agitated at 300 rpm while the receiver chambers were heated to a temperature of 37°C.

The donor chamber received the formulas. 0.5ml of solution in a receiver chamber was removed for GC analysis at 2, 4, 6, and 8 hours, and it was immediately replaced with an equal amount of fresh solution 18 at each of those times. Each sample was examined three times. To calculate the overall number of medicines penetrated at each time interval, cumulative adjustments were applied. Rat skin penetration of the total drug concentration was plotted with time function. The cumulative quantity penetrated through the rat skins per unit area against the time slope of the plot was used for computing the steady-state drug permeation rates via rat skin.[3]

(o) Thermodynamic stability Studies [22]

- **Heating-Cooling Cycle:** Formulations for nanoemulsions underwent six cycles at temperatures range of 4 to 45 degrees. The centrifugation test was then performed on the stable formulations.
- **Centrifugation:** The nanoemulsion formulations that did not phase separate during the 3500-rpm centrifugation were chosen for the freeze-thaw stress test.
- **Freeze Thaw Cycle:** Under standard laboratory conditions, the formulation was subjected to three freeze thaw cycles at s temperatures range of 21 to +25°C. These studies took place over a three-month period.

VI. APPLICATION OF NANOEMULSIONS:

(a) Parenteral Delivery

Due to this method of administration's strict criteria, notably the necessity for formulation droplet size smaller than 1ml, nanoemulsions are beneficial for intravenous administration. Nutrition is one of the many applications for parenteral nanoemulsion administration (fats, carbohydrates, vitamins, and so on). For parenteral drug delivery, lipid nanoemulsions have been extensively researched. When administered parenterally, nanoemulsion formulations offer a number of benefits over macroemulsion systems because fine particle nanoemulsion is removed more slowly than coarse particle emulsion and so has a longer residence period in the body. O/W and W/O Nanoemulsions both permit parenteral delivery. To administer medications with low bioavailability and/or therapeutic index, parenteral nanoemulsions are employed.[11]

(b) Ocular Delivery

O/W emulsions are being studied for their potential to improve topical lipophilic drug delivery to the eye. Following topical instillation into the eye, lipophilic drug-loaded o/w ocular emulsions such piroxicam, pilocarpine, indomethacin, and cyclosporine provide an optimum balance in patient comfort and ocular bioavailability improvement.[12,32]

(c) Oral Delivery

Nanoemulsions have been reported to be ideal for steroid, hormone, diuretic, and antibiotic drug delivery. Due to their less than 10% oral bioavailability in conventional (non-nanoemulsion-based) formulations, they are often not therapeutically effective when administered orally. Due to their poor oral bioavailability, the majority of protein medications are only accessible in parenteral formulations.[3,29]

(d) Intranasal Delivery

Intranasal drug delivery is currently acknowledged as a dependable route for drug administration, alongside parenteral and oral routes. Additionally non-invasive, painless, and well-tolerated, this approach. O lfactory region of the nasal mucosa connects the nose and the brain, and drug-loaded nanoemulsions can treat conditions like Migraine, Alzheimer's disease, Schizophrenia, Depression, Meningitis, Parkinson's disease, and others. Their usage in the development of therapeutic vaccines.[23]

(e) Transdermal Delivery

The nanoemulsion increases medication penetration through the skin by delivering water, an effective softener, to the skin. Nanoemulsion can therefore be utilised for transdermal drug delivery.[6] Many products are widely available in transdermal form so as to offer the patient with a more pleasurable experience. This route provides additional benefits such as first pass metabolism and the prevention of GI tract damage.[24,36,37]

(f) Topical Delivery

One advantage of topical drug administration over other methods is the avoidance of hepatic first pass metabolism and the toxicity effects related to it. The drug's ability to be administered directly to the area of skin or eyes that is affected is another advantage. Systemic antibiotics could not produce the same level of topical antibacterial activity as the nanoemulsion. The nanoemulsion is efficient against fungus, viruses, and bacteria including Staphylococcus aureus and E. coli (e.g., Candida, Dermatophytes) [9,38]

(g) In Cosmetics

A nanoemulsion has recently become a promising vehicle for controlled cosmetic delivery as well as optimised active ingredient dispersion in particular skin layers. Nanoemulsions are preferable to liposomes for the transfer of lipophilic compounds because of their internal lipophilicity. Because macroemulsions naturally cream, sediment, flocculate, and coalesce, nanoemulsions are appropriate for usage in cosmetics. It is frequently possible to prevent the integration of potentially irritating surfactants during manufacture by using high-energy equipment.[7,34,35]

(h) In Targeted Therapy

Most nano-systems are being researched in this scenario for distribution to the target site, including nanoemulsions, nanoparticles, liposomes, dendrimers, micelles, and nano-capsules. Targeted drug delivery is one of the benefits of nanoemulsion. Targeted delivery via specific cellular markers, whereas it has the potential to improve therapeutic agent efficacy while decreasing toxicity. Nanoemulsions are being studied for cancer prevention, detection, and treatment.[25]

CONCLUSION

For such medication, biological, or diagnostic agent administration, nanoemulsion formulations provide a variety of advantages, such as the ability to safeguard labile pharmaceuticals, control drug release, increase drug bioavailability, enhance drug solubility, and lessen patient variability. Since more than 40 years ago, clinics have employed nanoemulsions as fluids for whole parenteral feeding. Although nanoemulsions are most often used to distribute water insoluble pharmaceuticals, colloidal carriers have recently gained popularity for the targeted administration of certain anticancer treatments, diagnostic agents, photosensitizers, or neutron capture therapy agents. Their submicron size makes it possible to target the tumour directly. Additionally, because to the targeting component, there are now additional choices for the targeted administration of medications, genes, photosensitizers, and other substances to tumour locations.

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