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# Nanoemulsion for Delivery of Poorlysoluble Drug: A Review

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**Abstract:** *This review gives a brief overview of nanoemulsion formulation, methods, evaluation criteria, and pharmaceutical applications. The hydrophobic properties of the new chemical entities and the delivery of poorly water soluble drugs lead researchers to consider nanoemulsions. As the name implies, a nanoemulsion has extremely small particles that can easily pass through a variety of barriers to deliver the greatest amount of drug absorption to the site. These are two immiscible liquid phases that have been combined into a single stable isotropic phase using an emulsifying agent or surfactant, which reduces the interfacial tension between the two liquids.*

**Keywords:** Nanoemulsion, Microfluidization, Phase Inversion, Zeta Potential, Characterization

## I. INTRODUCTION

Nanoemulsions are now been used for delivery of antibiotics, topical, vaccines, DNA encoded drug and cosmetic preparations and there are different routes of administration like oral, intranasal, transdermal and pulmonary route etc by which the drug should be administered. Nanoemulsions are specified by its stability and clarity. [1] An excellent approach of drug delivery system has been developed to triumph over the major downside linked with the conventional drug delivery system. A nanoemulsion is adjudge to be a stable isotropic system of two immiscible liquid phases either thermodynamically or kinetically i.e., an oil phase and a water phase by means of an emulsifying agents. .[2] These are a colloidal particulate system in the submicron size variety performing as carriers of drug molecules. The size of the nanoemulsion ranges from10 to 200 nm and shows a narrow size distribution. An interfacial tension between the two liquids is present and surfactants or co- surfactants are used to diminish the interfacial tension. [3]

Depending on the composition, there are three types of nanoemulsions are formed i.e., oil in water (O/W) nanoemulsion, water in oil (W/O) nanoemulsion and bi-continuous nanoemulsion in which oil droplets are dispersed in the continuous aqueous phase, water droplets are dispersed in the continuous oil phase and microdomains of oil and water are interdispersed within the system respectively.[4] The appropriate combination of surfactant and co-surfactant is used to stabilize the interfacial tension between the phases.[5] Low carbonchain length oils are selected so that they can form stable system with amphiphiles. Nano sizeof the emulsion is depends on the concentration of the surfactants used. The deterioration process of emulsion i.e., creaming, flocculation, coalescence and sedimentation can be overcome by the use of nanoemulsion because of its stable nature.[6-7]

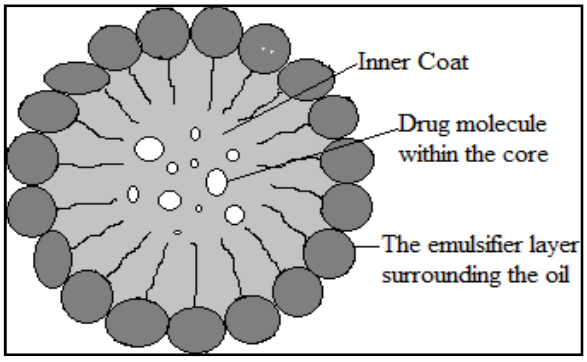


Fig 1: Structure of Nanoemulsion.

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### 1.1 Advantages[8-10]

The advantages of the nanoemulsions are as follows

- Nanoemulsion is an effective delivery system because of their more surface area and freeenergy than macro emulsions.
- Nanoemulsions are non toxic and non irritant so that it is acceptable to skin and mucousmembrane.
- Foams, creams, sprays and liquids are the various formulations can be formulated.
- Bio compatible surfactants are used for oral administration of the formulation.
- It is suitable for human and veterinary medication purposes.
- Creaming, flocculation, coalescence and sedimentation like problems should beovercome.
- It helps in solubilizing lipophilic drugs.
- Increases the rate of absorption hence increase bioavailability.
- It should carry both hydrophilic and lipophilic compounds.
- Minimizes side effects due to less total dose.

### 1.2 Disadvantages[11-12]

- For stabilizing the nano droplets, large concentration of surfactants and co-surfactantsshould be used.
- High cost for commercial preparations.
- Stability is affected by pH and temperature like parameters.
- It is difficult to understand the mechanism of production of sub micron droplets.
- For high melting substance, there is limited solubility.
- Large concentration of surfactants must be toxic.

### 1.3 Types of Nanoemulsion

Emulsions are classified due to their composition and morphological characters. Most likely three types of nanoemulsions are formed:

- Water in oil (w/o) nanoemulsion, where water is in dispersed phase and oil is incontinuous phase.
- Oil in water (o/w) nanoemulsion, where oil is in dispersed phase and water is incontinuous phase.
- Bi-continuous nanoemulsion, where microdomains of water and oil are interdispersedwithin the system.
- For stable nanoemulsion, surfactant, co-surfactant or combination of surfactant and co- surfactant should be used.[2,11]

## II. COMPONENTS OF NANOEMULSION

The main components of nanoemulsions are oil, surfactants/co-surfactants and aqueous phases.[13-15] Appropriate proportion of oil, surfactants/co-surfactants and aqueous phases are used in the manufacturing of nanoemulsions. The examples of oil, surfactants and co- surfactants used in nanoemulsions are mentioned in table 1, 2 and 3. For making transparent nanoemulsions, the droplet size of the dispersed phase should below 140 nm in diameter. Oil phase in any nanoemulsions plays an important role in selection of other ingredients in nanoemulsion. The selection of oily phase is also depends on its potency to dissolve with the drug candidate.[16-17]

Table 1: List of oils used in nanoemulsions.

| S.No. | Oils | Chemical Name |
|---|---|---|
| 1. | Capmul MCM | Glycerol monocaprylate |
| 2. | Capryol 90 | Propylene glycol monocaprylate |
| 3. | Captex 200 | Propylene Dicaprylate |
| 4. | Captex 355 | Glyceryl Tricaorylate/Caprate |
| 5. | Captex 8000 | Glyceryl Tricaprylate |
| 6. | Carbitol | Glycerol Triacetace |
| 7. | Isopropyl Myristate | Myristic acid isopropyl ester |

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| | | |
|---|---|---|
| 8. | Labrafac | Medium chain triglyceride |
| 9. | Maisine 35-1 | 1-Monolinolein |
| 10. | Myritol 318 | c8/c10 triglyceride |
| 11. | Peceol | Glyceryl Oleate |
| 12. | Sefsol 218 | Caprylic/ capric triglyceride |
| 13. | Witepsol | 90:10 % w/w c-12 glyceride tri:diesters |

Some modified vegetable oils, digestible and non digestible oils and fats are also used in the manufacturing of nanoemulsions.[18]

- Coconut oil
- Castor oil
- Corn oil
- Ethyl oleate
- Evening prime rose oil
- Linseed oil
- Methyl decanoate
- Olive oil
- Peanut oil
- Sesame oil
- Soya bean oil

The surfactant choice is depends on the nanoemulsion to be prepared. Water in oil (w/o) nanoemulsions are prepared with the surfactants which have HLB value less than 10 (HLB < 10) and oil in water (o/w) nanoemulsions are prepared with the surfactants which have HLB value more than 10 (HLB > 10).[19]

The surfactants which are used to stabilize the nanoemulsion are as follows:

- Anionic surfactants
- Cationic surfactants
- Non ionic surfactants
- Zwitter ionic surfactants

The surfactants used in combination mainly ionic and non ionic surfactants in the manufacturing of nanoemulsion are very effective at increasing the extent of the nanoemulsion region. Biocompatibility of zwitter ionic surfactants shows excellent results as compared to others.[20-22]

Table 2: List of surfactants used in nanoemulsion.

| S.No. | Surfactants |
|---|---|
| 1. | Capryol 90 |
| 2. | Cremophor RH 40 |
| 3. | Emulphor-620 |
| 4. | Gelucire 44/14, 50/13 |
| 5. | Imwitor 191, 380(1), 380, 742, 780 K, 928, 988 |
| 6. | Labrafil M 1944 CS, M 2125 CS |
| 7. | Lauroglycol 90 |
| 8. | PEG MW > 4000 |
| 9. | Plurol Oleique CC 497 |
| 10. | Polaxmer 188 |
| 11. | Poloxamer 124 and 188 |
| 12. | Poloxamer 407 |
| 13. | Softigen 701, 767 |
| 14. | Tagat TO |
| 15. | Tween 80 |

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When surfactant fails to lower the interfacial tension between oil and water to form a stable nanoemulsion then co-surfactants are used. Co-surfactant works by disrupting the liquid crystalline phase by penetrating into the monolayer of the surfactant and also provides extra fluidity.[23]

Table 3: List of Co-surfactants used in nanoemulsion.

| S.No | Co-surfactants |
|---|---|
| 1 | Apricot kernel oil PEG-6 esters |
| 2. | Diethylene Glycol Monoethyl ethers |
| 3. | Ethanol |
| 4. | Glycerine, Ethyl Glycol |
| 5. | Medium chain mono and diglycerides of caprylic acid |
| 6. | Polyglyceryl Oleate |
| 7. | Propylene Glycol Monolaurate |
| 8. | Propanol |
| 9. | Transcutol P |

## III. FORMULATION ASPECTS AND PREPARATION METHODS OF NANOEMULSION

Nanoemulsion formulation includes active pharmaceutical ingredients, additives andsurfactants. Co-surfactants are also used if necessary in the formulation of nanoemulsion. Mainly there are two methods which are used in the manufacturing of nanoemulsions.

1. High energy emulsification includes microfluidization, membrane emulsification, high pressure homogenization, high energy stirring and ultra sonic emulsification.[24-25]
2. Low energy emulsification includes emulsion inversion point, spontaneous emulsificationand phase inversion temperature.[26]

### 3.1 Microfluidization

A device called microfluidizer is used for this process which works on mixing technique. It uses high pressure displacement pump which forces the product through the interaction chamber consisting of microchannels which results in a very fine particles of sub micron range. The repetition of process is continued until desired particle size obtained. The process of micofluidization is shown in fig 1. Under the presence of nitrogen the large droplets are removed from the bulk emulsion by filteration process.[27-28]

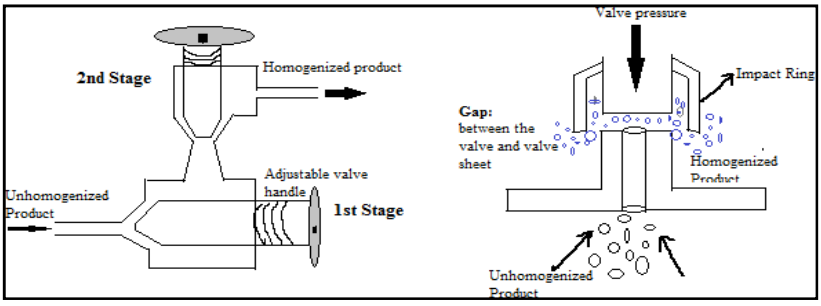


Fig 1: Process of Microfluidization.

### 3.2 High Pressure Homogenization

The equipment used in this process is known as high pressure homogenizer or piston homogenizer which produces nanoemulsions of about 0.1 nm in size. The dispersion of both oily phase and aqueous phase is attained by forcing their mixture through a small inlet orifice at very high pressure which creates intense turbulence and hydraulic shear and particularly responsible for very fine particles of emulsion. The high pressure homogenizer is shown in fig 2. Some process variables should also be conduct for the preparation of optimized nanoemulsion.[29-30]

- Number of homogenization cycle
- Effect of homogenization pressure

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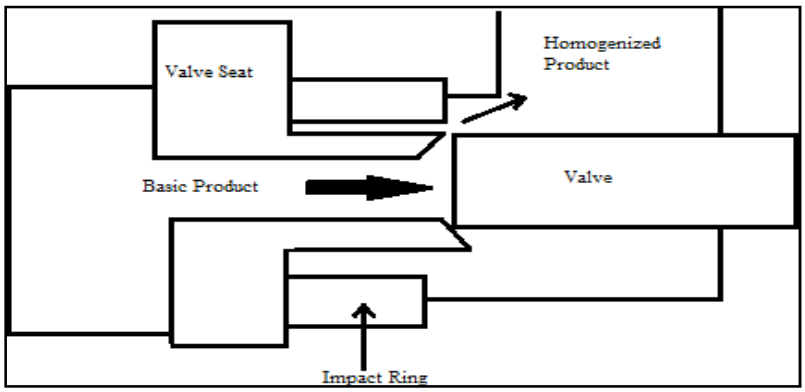

Fig 2: Formation of nanoemulsion by high pressure homogenizer.

### 3.3. Ultrasonic Emulsification

For reduction of the globule size of the nanoemulsions, ultrasonic sound frequency can be used. The energy in ultrasonic emulsification is provided by sonotrodes or called as sonicator probe. In sonotrodes there is piezoelectric quartz crystal which can be contract and expand in reaction to alternating electrical voltage. As the tip of sonicator probe contacts the liquid it forms and sudden collapse of vapour cavities in the flowing fluid due to mechanical vibrationgeneration and this formation and collapse of vapour cavities in the flowing fluid is known ascavitation. The equipment used in this process is shown in fig 3. It is better to prepare coarse emulsion because a large sum of energy is essential in the breakdown of an interface. To maintain the temperature at optimum level water jacket must be used.[31-32]

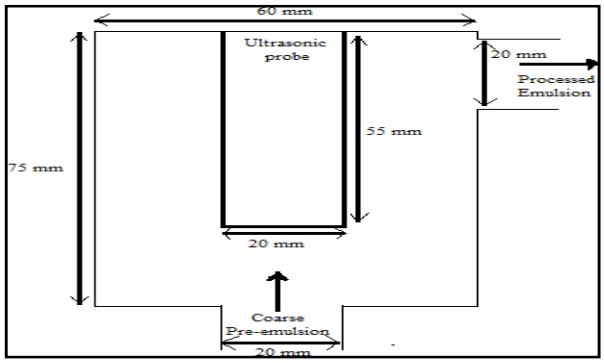

Fig 3: Schematic of ultrasonic emulsification.

### 3.4 Membrane Emulsification

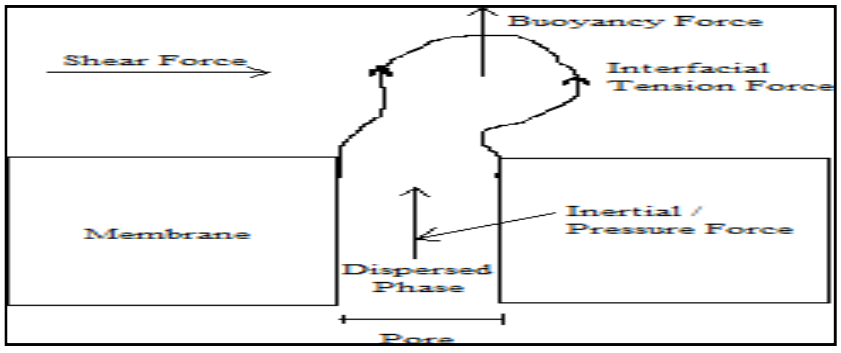

Fig 4: Forces acting on the droplets during membrane emulsification.

The mechanism of droplet formation in membrane emulsification involves two stages i.e., droplet growth and droplet detachment.[33] Emulsions formed with the help of membrane can be achieved by means of a regular droplet detachment from the pore outlets where a shear stress is generated at the continuous phase interface and then recirculating the

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continuous phase with the help of stirring vessel or low shear pump. Four main forces are required for the droplet detachment at the membrane i.e, shear force, interfacial tension force, inertial / pressure force and buoyancy force. The forces acting on the droplets are shown in fig 4. Buoyancy force assumed to be negligible because droplet is expected to be much smaller in magnitude.[34]

### 3.5 Emulsion Inversion Point

In this method, ratio of oil and water is more important than the properties of surfactant. The main step in this method is the transition between water in oil (w/o) and oil in water (o/w) emulsions via an intermediate bi continuous phase by continuously mixing of dispersed phaseof water into oil in water (o/w) emulsion initially formed and vice versa.[35-36] By adding water to the liquid crystalline phase we can formulate nanoemulsion but this process should be done at slow rate because rapid dilution can induce coarse emulsion with larger droplet size.[37]

### 3.6 Spontaneous Emulsification

It involves certain steps i.e.,

1. Preparation of uniform organic solution which is composed of oil and lipophilic surfactant in hydrophilic surfactant and water miscible solvent.
2. Oil in water (o/w) emulsion was formed by injecting organic phase in the aqueous phase with the use of magnetic stirrer.
3. Evaporation under reduced pressure was done to remove water miscible solvent.[38-39]

### 3.7 Phase Inversion Temperature

This method depends on change in molecular geometry of non ionic small molecule surfactants with changing temperature. The temperature at which a system changes from a oil in water emulsion (o/w) to water in oil (w/o) emulsion and vice versa with changes in the molecular geometry or solubility is called as phase inversion temperature and the ability of surfactants to change the system is associated with the critical packing parameter (CPP).[40] The ability of surfactant to self assemble to form a surfactant monolayer with respect to their molecular geometry is known as critical packing parameter. From following equation, it can be calculated:

$$CPP = \gamma / a l_c \quad (1)$$

Where $\gamma$= partial molar volume of the hydrophobic tail of surfactanta= surface area of the surfactant head group
$l_c$= hydrophobic chain length of surfactant tail group. The process of preparing nanoemulsion by phase inversion temperature is shown in fig 5.

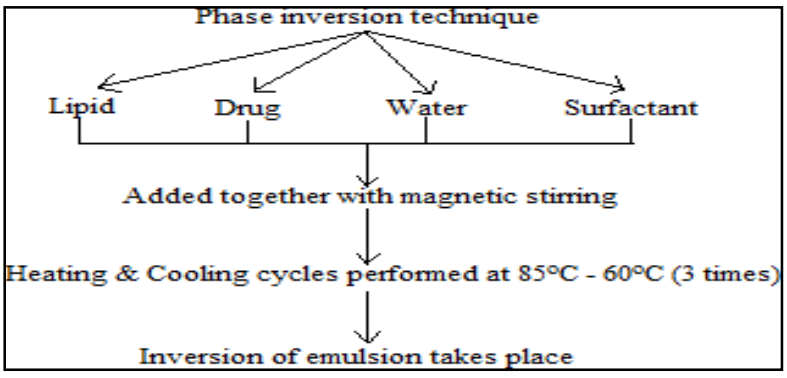


Fig 5: Preparation of nanoemulsion by phase inversion temperature.

**Factors concerning with the preparation of nanoemulsion[41]**

- The primary requirement to produce nanoemulsion is ultralow interfacial tension. So, toachieve this state we have to select surfactant carefully.
- The surfactant must be flexible to support the formation of nanoemulsion.
- To stabilize the nanoemulsion, the concentration of the surfactant must be high enough.

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## V. EVALUATION AND CHARACTERIZATION OF THE PREPARED NANOEMULSIONS

Different characterization parameters of nanoemulsions are.

### 5.1 Droplet Size

The best method for predicting nanoemulsion stability is to analyze the droplet size of the formulation. Mainly scanning electron microscopy using scanning electron microscope and light scattering technique using zeta size which measuresthe Brownian motion of the particles.[42]

### 5.3 Refractive Index

Abbes type refractometer is used for the determination of refractive index of the prepared nanoemulsion.

### 5.3 Zeta Potential Analysis

he degree of electrostatic repulsion between charged particles in dispersion is analyzed by zeta potential of that formulation.

**Table 4:** Values of zeta potential.

| S.No. | Zeta Potential (mV) | Stability Behavior |
|---|---|---|
| 1. | More than ± 61 | Excellent Stability |
| 2. | ±40 to ±60 | Good Stability |
| 3. | ±30 to ±40 | Moderate Stability |
| 4. | ±10 to ±30 | initial Stability |
| 5. | 0 to ±5 | Rapid Coagulation |

### 5.4 Polydispersity Index

It is used to detect the uniformity of droplet size within the formulation. Ratio of standard deviation to mean droplet size is known as polydispersity. Polydispersity is inversely proportional to uniformity of the droplet size in the formulation.[43-45]

### 5.5 Drug Content and Percentage Transmittance

The amount of drug is calculated by making dilutions in a suitable solvent and then analyzed with the help of U V spectrophotometer or HPLC. Percentage transmittance of the nanoemulsion is also measured by a UV-Visible spectrophotometer.[46]

### 5.6 Fluorescence Test

In this test, the nanoemulsion is examined under the microscope in exposure of UV light. If fluoresces observed in the nanoemulsion then it is water in oil nanoemulsion and if not or spotty fluoresces occurs then it is oil in water nanoemulsion.

### 5.7 Filter Paper Test

In this test, the nanoemulsion is dropped on to a filter paper, if it spreads rapidly then it is oil in water nanoemulsion and if not then it is water in oil nanoemulsion.[47]

### 5.8 Conductivity Test

Conductometer is used to measure the conductance of the nanoemulsion. We all know that oilis a non conductor and water is a good conductor of electricity. Therefore, if water is in continuous phase then bulb glows and if oil is in continuous phase then bulb not glows as shown in fig 6.

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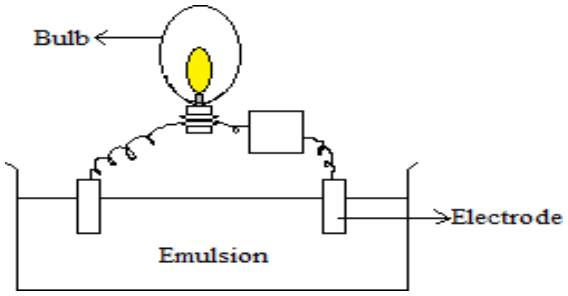


Fig 6: Conductivity test.

## VI. APPLICATIONS OF NANOEMULSIONS[48-51]

There is broad range of applications of nanoemulsions in pharmaceutical or biomedicalapplications given in fig 7.

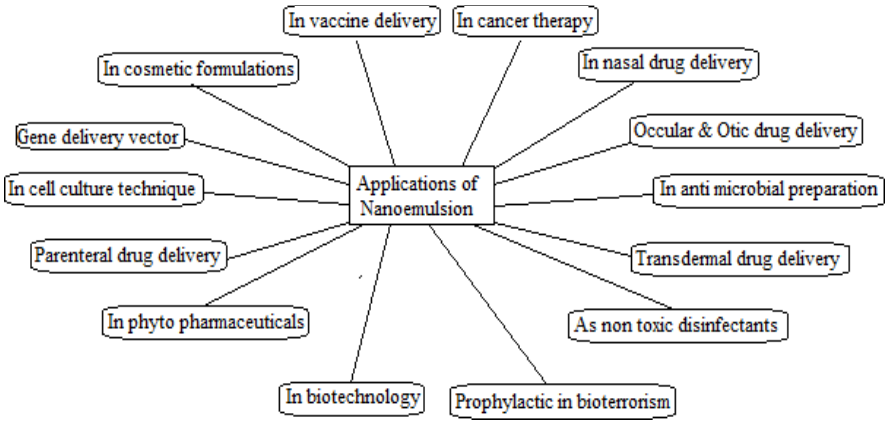


Fig 6: Applications of Nanoemulsion.

There are many barriers in the direct entry of drug to the target site so nasal route offers the best way to deliver the drug to the site. This route offers painless drug delivery. Because of its high availability of immunoreactive sites, reduced enzymatic activity and permeable epithelium, nasal cavity becomes most effective site for drug delivery.

Drugs having low bioavailability and narrow therapeutic index is delivered via most common route called parenteral route. Nanoemulsions are ideal to parenteral route because of their mutual compatibility and ability to protect the drug from hydrolysis and enzymatic degradation.

For poorly soluble drugs oil in water nanoemulsions are used for ocular delivery of the drug and is also increase the absorption and release sustainably.

Nanoemulsions are also very effective in transdermal delivery mainly for cosmetics because of the low viscosity, droplet size and transparency of the formulation. But we have to take care that use of irritating surfactants must be avoided during the manufacture of nanoemulsion for cosmetic use. Because of the very low particle size of the nanoemulsion, the penetrating and spreading power of the formulation increases.

It is very difficult to provide the media with oil soluble substances that are available to the cells due to very small amounts of the lipophilic compounds could be absorbed by the cell. So a new technique for the delivery of oil soluble substances to human cell cultures was developed with the use of nanoemulsion. By the use of nanoemulsion in cell cultures, the better uptake of oil soluble supplements in cell cultures occurs. A toxicity study of oil solubledrugs in cell culture is possible.

## VII. RECENT ADVANCEMENTS IN NANOEMULSION

| S.No. | Recent Work | Description |
|---|---|---|
| 1. | The Efficacy of Nanoemulsion-Based Delivery to Improve Vitamin D Absorption: Comparison of in Vitro andin Vivo Studies. | Using simulated GIT system, examination ofphysical as well as *in vitro* characteristics of cholecalciferol in nanoemulsion was done.[52] |

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| 2. | ω-3 Fatty Acid Synergized Novel Nanoemulsifying System for Rosuvastatin Delivery: In Vitro and InVivo Evaluation. | Prepared synergized novel nanoemulsifying system using perilla frutescens oil as lipid carrier to enhance the bioavailability and pharmacologivcal response of rosuvastatin.[53] |
| 3. | Nanoemulsion of dill essential oil as agreen and potent larvicide against anopheles stephensi. | Formulated nanoemulsion using dill essential oilto see the larvicidal effects of Anopheles stephensi. Tween 20 was used as a surfactants inthis formulation. The formulation was also prepared for the first time.[54] |
| 4. | Enhancement of Anti-Inflammatory Properties of Nobiletin in Macrophagesby a Nanoemulsion preparation. | Nanoemulsion was prepared using Nobiletin, a hydrophobic crystalline bioactive compound and found enhanced activity of anti inflammatory action.[55] |
| 5. | Effect of high pressure homogenization on the structure and the interfacial and emulsifying properties of β- lactoglobulin. | Properties of β-lactoglobulin were tested for the emulsification and interfacial tension using high pressure homogenization.[56] |
| 6. | Development of triptolide-nanoemulsion gels for percutaneous administration: physicochemical, transport, pharmacokinetic and pharmacodynamic characteristics. | Prepared nanoemulsion gel of triptolide for the percutaneous administration and found improvement in the symptoms of eczema and dermatitis.[57] |
| 7. | Formulation Development and Evaluation of the Therapeutic Efficacy of Brinzolamide Containing Nanoemulsions. | Brinzolamide containing nanoemulsions shows better bioavailability and reduces the intraocularpressure.[58] |
| 8. | An optimized two-vial formulation lipid nanoemulsion of paclitaxel for targeted delivery to tumor. | Paclitaxel loaded nanoemulsion was prepared for intravenous delivery for anticancer activity and found suitable[59] |
| 9. | Nanoemulsions of sulfonamide carbonic anhydrase inhibitors strongly inhibit the growth of Trypanosoma cruzi. | Sulfonamide carbonic anhydrase inhibitor encapsulated in the nanoemulsion shows inhibition in the life cycle of protozoan pathogen Trypanosoma cruzi by permeation of the enzymeinhibitor.[60] |
| 10. | Formulation optimization and the absorption mechanisms of nanoemulsion in improving baicalin oral exposure. | Prepared nanoemulsion containing baicalin administered orally and increases the intestinal absorption and lymphatic transport process which also results in increased bioavailabilty.[61] |

Table 5: Recent advancements.

## VIII. MARKETED FORMULATIONS[62]

Nanoemulsions market formulation is given in table no. 6.

Table 6: Marketed nanoemulsion formulations.

| S.No. | Brand Name | Drug | Use | Manufacturer |
|---|---|---|---|---|
| 1. | Dipriven | Propofol | Anaesthetic | Astra Zaneca |
| 2. | Etomidat-Lipuro | Etomidate | Anaesthetic | B. Braun melsungen |
| 3. | Gengraf | Cyclosporin A | Immunosupresant | Abbott Pharma |
| 4. | Limethason | Dexamethason | Steroid | Mitshubishi pharmaceutical |
| 5. | Liple | Alprostadil palmitate | Vasodilator/ platelet inhibitor | Mitshubishi pharmaceutical |
| 6. | Norvir | Ritonavir | Anti retroviral | Abbott Pharma |
| 7. | Restatis | Cyclosporin A | Immunosupresant | Allergan |
| 8. | Ropion | Flurbiprufen axtin | NSAID | Kaken Pharmaceutical |
| 9. | Troypofol | Propofol | Anaesthetic | Troikaa |
| 10. | Vitalipid | Vitamin A, D, E & K | Parenteral Nutrition | Fresenius Kabi |

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## IX. CONCLUSION

We can infer from this review that nanoemulsion offers a variety of delivery options for the formulation. For less soluble drugs, it has many benefits. Additionally, it works well for the controlled and targeted delivery of medications. The external environment protects the drug that is encapsulated. Future research and development on nanoemulsion in the various therapeutic fields will focus primarily on toxicity studies of the nanoformulation that is created by using an excessive amount of surfactant

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