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A REVIEW: FORMULATION AND EVALUATION OF NANOEMULSION FOR TOPICAL DRUG DELIVERY SYSTEM USING MODEL DRUG

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ABSTRACT

Nanoemulsion is an advanced mode of drug delivery system has been formulated and developed to overcome the major drawbacks associated with conventional drug delivery systems. In this review it gives a detailed about a nanoemulsion system. Nanoemulsions are submicron emulsion, nanosized emulsions, which are manufactured for improving the delivery of active pharmaceutical ingredients. These are transparent and thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, surfactant and co-surfactant. The droplet size of nanoemulsion is in the range 20–200 nm. The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase. In this review, the attention is focused to give a basic idea about its formulation, method of preparation, characterization techniques, evaluation parameters, and various applications of nanoemulsion.

KEYWORDS: Nanoemulsion, Oil, Surfactant, Co-surfactant.

INTRODUCTION

Nanoemulsions are more stable than conventional emulsions because their small droplet sizes allow them to pass through delicate capillaries and penetrate deep into the tissues. As a result, this is being thoroughly studied for its potential as a drug delivery system and for its capacity to target particular body regions. Nanoemulsion is one of the most effective dosage forms for reaching the target and has received a lot of attention recently for its use in a variety of industries. As a medication delivery mechanism for a variety of systemic routes, including oral, topical and parenteral, nanoemulsions are used.

A transparent, thermodynamically stable mixture of two non-soluble liquids, such as oil and water, stabilised by an interfacial surfactant coating is referred to as a nanoemulsion. Using an emulsified oil and water system with a mean droplet size that spans from 50 to 1000 nanometers (nm), nanoemulsions are a revolutionary medication delivery technology. Nanoemulsions are submicron sized colloidal particulate systems that contain two immiscible liquids, such as water and oil, and are stabilized by an interfacial film made of an appropriate surfactant and co-surfactant to form one phase. They are also referred to as submicron emulsions, ultrafine emulsions, and mini emulsions. Nanoemulsions have been employed with a variety of surfactants, some of which have different properties (ionic or non-ionic) surfactant.[1]

Nanoemulsion defined as a colloidal dispersion of two immiscible liquids that is thermodynamically unstable with each other. The nanoemulsion coatings can also prevent moisture and gas exchange, minimize moisture loss and oxidation of foods.[2]

Nanotechnology is developing rapidly in many sectors, especially cosmetics, pharmaceutics, agriculture and food industries. Most of these interests are geared toward the development of lipophilic substances like fatty acids, favors, colors, and drugs. The need for using nanotechnology/nanoparticles in emulsion fabrication is crucial because emulsions have been produced from numerous ingredients and additives for so many years, creating markets and profitability.[3]

Nanoemulsions are a colloidal particulate system in the submicron size range acting as carriers of drug molecules. Their size varies from 10 to 1,000 nm. These carriers are solid spheres and their surface is amorphous and lipophilic with a negative charge. Magnetic nanoparticles can be used to enhance site specificity. As a drug delivery system, they enhance the therapeutic efficacy of the drug and minimize adverse effect and toxic reactions. Major application includes treatment of infection of the reticuloendothelial system (RES), enzyme replacement therapy in the liver, treatment of cancer, and vaccination. An emulsion is a biphasic system in which one phase is intimately dispersed in the other phase in the form of minute droplets ranging in diameter from 0.1 to 100 lm. It is a thermodynamically unstable system, which can be stabilized by the presence of an emulsifying agent (emulgent or emulsifier). The dispersed phase is also known as internal phase or the discontinuous phase while the outer phase is called dispersion medium, external phase or continuous phase. The emulsifying agent is also known as intermediate or interphase. The term 'nanoemulsion' also called miniemulsion which is fine oil/water or water/oil dispersion stabilized by an interfacial film of surfactant molecule having droplet size range 20–600 nm.[4]

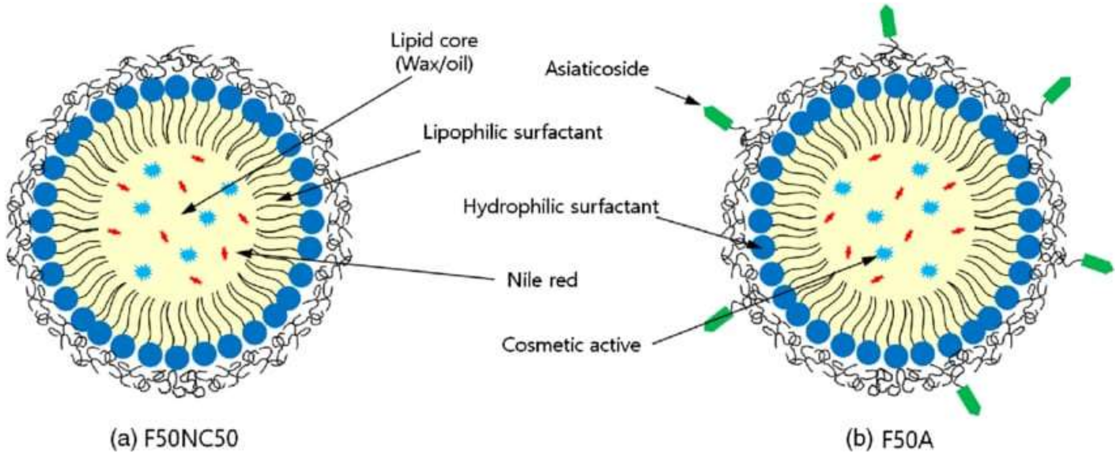

Figure 1: Composition of nanoemulsion.

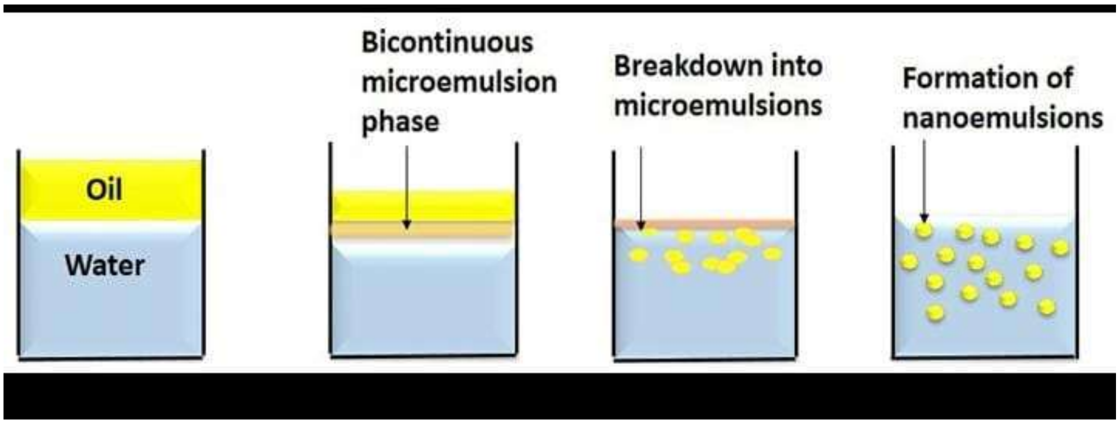

Figure 2: Formation of nanoemulsion.

Advantages of nanoemulsion

- Increase the rate of absorption
- Eliminates variability in absorption
- Helps to solubilize lipophilic drug
- Provides aqueous dosage form for water insoluble drugs
- Increases bioavailability of active drug
- Rapid and efficient penetration of the drug moiety
- Helpful in taste masking

- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W

Nanoemulsion is not exposed to attack by water and air

- Liquid dosage form increases patient compliance
- Less amount of energy requirement
- Nanoemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed
- Improve the efficacy of a drug, allowing the total dose to be reduced and thus
- Minimizing side effects

Disadvantages of nanoemulsion

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets
- Limited solubilizing capacity for high-melting substances
- The surfactant must be nontoxic for using pharmaceutical applications
- Nanoemulsion stability is influenced by environmental parameters such as temperature and ph. These parameters change upon Nanoemulsion delivery to patients

Factors to be considered during preparation of nanoemulsion

1. Surfactant must be selected carefully such that an ultralow interfacial tension may be achieved which is a primary requirement to produce nanoemulsion.
2. Concentration of surfactant must be high enough to stabilize the microdroplets to produce nanoemulsion.
3. The surfactant must be flexible or fluid enough to promote the formation of nanoemulsion.[4]

Characterization of nanoemulsion[2]

A thermodynamically stable nanoemulsion is characterized by the absence of the internal phase, absence of creaming, absence of deterioration by microorganisms, and maintenance of elegance in respect of appearance, color, Oduor and consistency hence the instability of emulsion can be classified as follows.

Flocculation and Creaming

Flocculation consists of the joining together of globules to form large clumps or floccules, which rise or settle in the emulsion more rapidly than the individual globules.

The rising up or settling down of dispersed globules to give a concentrated layer is known as creaming thus flocculation leads to creaming.

Cracking

Cracking of an emulsion refers to separation of the dispersed phase as a layer whereas a creamed emulsion may be reconstituted by shaking or agitation, a cracked emulsion cannot be corrected.

Cracking represents permanent instability.

Cracking of the emulsion may be due to

(1) Addition of an emulgent of opposite nature,
(2) Decomposition or precipitation of emulgent,
(3) Addition of a common solvent in which both oily and aqueous phases are miscible,
(4) Extremes of temperature,
(5) Microorganisms,
(6) Creaming

Miscellaneous instability

Emulsions may deteriorate if stored under extremely high or low temperature or in presence of light. Hence emulsions are usually packed in air-tight, colored containers and stored at moderate temperature.

Phase inversion

It is the change in the type of emulsion from o/w to w/o and vice versa it is the physical process. Phase inversion may be brought about by varying the phase volume ratio, addition of electrolytes, and temperature changes.[4]

Components of nanoemulsion

Main three components of Nanoemulsions are as follows

- Oil
- Surfactant/Co-surfactant
- Aqueous phase [8]

Table 1: Components of nanoemulsion.

Component	Examples
Oil	Castor oil, Coconut oil, Corn oil, Linseed oil, Peanut oil, Evening prime rose oil, Mineral oil, Olive oil, Groundnut oil.
Surfactant	Polysorbates, Polysorbate20, Polysorbate80, Sterylamine, Polyoxy 60, Sorbitan monooleate, Caprylic glyceride, PEG300.
Co-surfactant	Ethanol, Glycerine, PEG300, PEG400, Polyene glycol, Poloxamer.
Emulgent	Castor oil derivatives, Natural lecithin from plants or animal, Phospholipids.
pH Stabilizer	Sodium hydroxide or Hydrogen Chloride, Triethanolamine.
Tonicity modifiers	Sorbitol, Glycerol, Xylitol.
Antioxidants	Tocopherol, Ascorbic acid.
Preservatives	Methyl Paraben, Pottasium Sorbate, Propyl Praben, Benzalkonium Chloride.
Additives	Ethanol, Propylene glycol, 1,3-butylenes glycol, Sugars like glucose, Sucrose, Fructose and Maltose.

Nanoemulsion types[3]

I. **Water in oil nanoemulsion (W/O):** A droplet of water was distributed in a Continuous phase of oil during a nanoemulsion.

II. **Oil in water nanoemulsion (O/W):** Oil droplets were dispersed in a continuous phase of water during a nanoemulsion.

III. **Bi-continuous nanoemulsion:** In this process, the surfactant was soluble in both the water and the oil phases, and the droplet was distributed in both.

Techniques of preparation of nanoemulsions

The most used methods for producing nanoemulsions are as follows

- High-Pressure Homogenization
- Microfluidization
- Ultrasonication
- Phase inversion method
- Spontaneous Emulsification
- Solvent Evaporation Technique
- Hydrogel Method

1. High-Pressure homogenization

Nanoemulsion preparation required high pressure homogenization. In this method high-pressure homogenizer/ piston homogenizer is used to produce nanoemulsions of extremely low particle size (up to 1 nm). The dispersion of two phases (oil and aqueous phase) is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion.[4]

2. Microfluidization

Microfluidization is a technology, in which microfluidizer is use as a device. Device uses a high-pressure positive displacement pump (500 - 20,000 psi), which forces the product through the interaction chamber, consisting of small channels called "microchannels". The product flows through the micro- channels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion.[5]

3. Ultrasonication

In Ultrasonication emulsion is exposed to agitation at ultrasonic frequency of 20 kHz reducing the droplets to nanodroplets size. The emulsion is then passed through high shear region to form droplets with uniform size distribution. To regulate the temperature Water jacket is employed.

Sonotrodes also known as sonicator probe consisted of piezoelectric quartz crystals as the energy providers during ultrasonic emulsification.[6]

4. Phase inversion technique

Phase inversion temperature technique shown a relationship between minimum droplet size and complete solubilization of the oil in a microemulsion by continuous phase independently of whether the initial phase equilibrium is single or multiphase. Due to small droplet size nanoemulsions possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. Phase inversion temperature (PIT) method employs temperature dependent solubility of nonionic surfactants, such as polyethoxylated surfactants, to modify their affinities for water and oil as a function of the temperature.[6]

5. Spontaneous emulsification

In spontaneous emulsification nanoemulsion is spontaneously formed. In this, preparation of homogeneous and uniform organic solution consisting oil and lipophilic surfactant in water miscible surfactant and hydrophilic surfactant phase. Then the organic phase was injected in aqueous phase under continuous magnetic stirring, stable o/w is formed. The aqueous phase was removed by evaporation under reduced pressure.[5]

6. Solvent evaporation technique/hydrogel method

In solvent evaporation technique technique, drug solution is prepared and emulsified into another liquid (Non-solvent for drug) and then solvent is evaporated, which led to drug precipitation. High speed stirrer can be employed for regulating the crystal growth and particle aggregation. Hydrogel method is very similar the solvent evaporation method. The only difference from the solvent evaporation method is that the drug solution in this case is miscible with the drug antisolvent.[6]

Evaluation test

1. Drug content
2. Viscosity
3. Droplet Size and Shape
4. Rheology
5. Polydispersity
6. pH
7. Dilution test
8. Dye test
9. Fluorescence test
10. Globule size and Zeta potential analysis
11. Centrifugation
12. Physical stability of drug
13. Drug Release Study.[4,7]

Patents on nanoemulsion

Table 2: Patents on nanoemulsion.

Application no	Title	Inventors	Year of Publication and Grant
US-10413966-B2	Nanoparticles having magnetic core encapsulated by carbon shell and composites of the same.	Sankaran Murugesan, Oleksandr Kuznetsov, Valery Khabashesku	2019

US-10016364-B2	Compositions and methods for making and using nanoemulsions.	Robert James NICOLOSI, Thomas Wilson	2018
US-9844679-B2	Nanoparticle-sized magnetic absorption enhancers having three-dimensional geometries adapted for improved diagnostics and hyperthermic treatment.	Joseph N. Nayfach-Battilana	2017
US-9149440-B2	Nanoparticles for drug-delivery.	Edward Turos, Jeung-Yeop Shim	2015
US-8822385-B2	Nanoemulsions.	Lirio Quintero, David E. Clark, Alexander John mckellar	2014

Marketed products of nanoemulsion

Table 3: Marketed product list of nanoemulsion.

Product Name	Drug	Manufacturer	Use
Diprivan, Troypofol	Propofol	Astra Zaneca	Anaesthetic
Liple	Alprostadil Palmitate	Mitsubishi pharmaceutical	Vasodilator, Platelet Inhibitor
Limethason	Dexamethason	Mitsubishi pharmaceutical	Steroid
Ropion	Flurbiprofen axtil	Kaken pharmaceutical	NSAID
Vitalipid	Vitamin AD, E and K	Fresenius kabi	Parenteral nutrition
Etomidat-lipuro	Etomidate	B. Braun melsungen	Anaesthetic
Voltaren Emulgel	Diclofenac diethylamine	Novartis Consumer Health	Anti-Infammatory
Restasis,gengraf	Cyclosporine	Allergen, abott	Immunosuppresant
Norvir	Ritonavir	abbott	Antiretoviral

Research work carried out on nanoemulsion

Table 4: Research work carried out on nanoemulsion.

Name of author	Name of study	Major findings	Year
Roswanira Wahab et al.	An overview of nanoemulsion concepts of development and cosmeceutical applications	To achieve stable nanosized emulsion.[9]	2019
Vijayendra Swamy et al.	Formulation and Evaluation of Nanoemulsion for	Nanoemulsion formulation for solubility enhancement.[10]	2019

	Topical Application		
Vasiliki Pletsa et al.	Development and study of Nanoemulsions and Nanoemulsion – Based hydrogels for the encapsulation of lipophilic compound	Nanoemulsion –based hydrogels formulated for the encapsulation and delivery of Vitamin D_3 and curcumin.[11]	2020
Sunny Antil et al.	Formulation and Evaluation of Nanoemulsion for Bioavailability enhancement of Metaxalone	Due to small droplet size there is no aggregation between the droplets. By using suitable technique gave improved drug release and also improved bioavailabilty.[12]	2021
Sajad Wani et al.	Recent insights into Nanoemulsion: Their preparation, properties and application	Emulsion based coating approach has been regarded as viable way to extent the shelf life of fresh Produce.[13]	2023

Applications of nanoemulsion

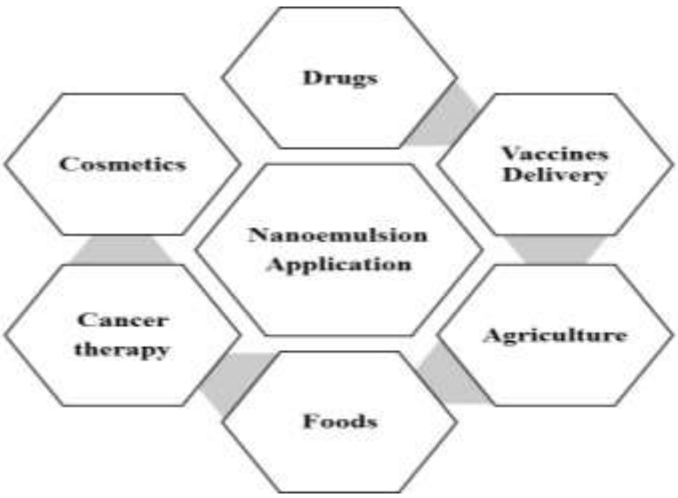

Figure 3: Figure comprises application of nanoemulsion.

CONCLUSION

Nanoemulsions most widely used in pharmaceutical systems. It includes several advantages such as delivery of drugs, biological or diagnostic agents. The important application of nanoemulsion is masking the disagreeable taste of oily liquids. It also protects the drugs, which are susceptible to hydrolysis and oxidation. Nowadays, nanoemulsions are used for targeted drug delivery of various anticancer drugs, photo sensitizers or therapeutic agents. Nanoemulsion can also provide prolonged action of the medicaments. All nanoemulsion formulation may be considered as effective, safe and with increased bioavailability. The further research and development of nanoemulsion will be carried out in the future. On the basis of their physicochemical and functional properties, nanoemulsions are use in healthcare, food, polymer manufacturing and cosmetics industries. To formulate nanoemulsions often employ emulsifers/surfactants and nanoparticles, which have raised eyebrows regarding their safety because they accumulate both in the environment and in the human body.

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