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Nanoemulsion: A Novel Approach for Enhanced Therapeutic Profile

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ABSTRACT

Drug administration is preferred mostly through oral, topical, and parenteral routes. Poor bioavailability by these routes is noticeable with the majority of new active pharmaceutical ingredients due to its dissolution rate-limited absorption. Failure to accomplish the proposed therapeutic effects of the poorly water-soluble drugs by these routes directed the development of a new drug delivery system that will accomplish therapeutically. Nanoemulsions are submicron-sized emulsions that act as drug carriers for improving the delivery of therapeutic agents. In pharmaceutical observation, nanoemulsion is one of the chief dosage forms in delivering active ingredients to the objective area which has engrossed great attention in recent years for its application in various fields. In the pharmaceutical field, nanoemulsions have been used as a drug delivery system through various routes such as oral, topical, and parenteral. Nanoemulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water, surfactant, and co-surfactant. These are oil-in-water (o/w) types of emulsions with the average droplet size ranging from 5nm to 100 nm. The present review provides comprehensive information on the advantages, disadvantages, methods of preparation, characterization techniques, applications, recent advances in the field.

INTRODUCTION:

Nanoemulsions emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. The type of surfactant used in the system determines which phase is continuous. If the surfactant is hydrophilic, then oil will be emulsified in droplets throughout a continuous water phase, the opposite is true from more lipophilic surfactants. Water will be emulsified in droplets that are dispersed throughout a continuous oil phase. Nanoemulsions are categorized as a multiphase colloidal dispersion and are characterized by its stability and clarity. The dispersed phase typically comprises small particles or droplets, and they have very low oil/water interfacial tension. Nanoemulsions are formed spontaneously and readily and sometimes generally without high-energy input. In many cases, a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase, and the water phase.[1-5]

Nanoemulsion has the potential to overcome several disadvantages in drug formulation. Loading poor water-soluble drugs in the appropriate nanoemulsions enhances their wettability and/or solubility. Consequently, this improves their pharmacokinetics and pharmacodynamics by different routes of administration. Associated with the optimum nanodroplet size or even combined with key components, the droplets act as a reservoir of drugs, enabling nanoemulsion to be a multifunctional platform to treat diverse diseases. Several important advantages, which comprise nanoemulsion attributes, such as efficient drug release with appropriate rate, prolonged efficacy, drug uptake control, low side effects, and drug protection properties from enzymatic or oxidative processes, have been reported in last decade. The high flexibility of nanoemulsion includes also a variety of manufacturing process options and a combination of widely assorted components such as surfactants, liquid lipids, or even drug-conjugates. These features provide alternatives for designing innovative nanoemulsions aiming at high-value applications[20].

Principle of nanosponges preparation:

Nanoparticles are available in various forms like polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, micellar systems, dendrimers etc[21]. Nanosponges are solid. They are found to be safe for oral and invasive routes; hence they can serve as an inherent carrier for drug delivery[22-24] Nanosponges are a novel class of

hyper-crosslinked polymer-based colloidal structures consisting of solid nanoparticles with colloidal and nanosized cavities. Some of the well-known nanosponges are titanium-based nanosponges, silicon nanosponge particles, hyper-crosslinked polystyrene nanosponges, and cyclodextrin based nanosponges. By reacting polyesters (cyclodextrins) with appropriate crosslinking agents, a novel nanostructured material can be obtained, known as nanosponges.[22]

The cyclodextrin to crosslinker ratio can be varied throughout the preparation period by improving the drug loading capacity and ultimately acquiring a tailored release profile. Highly porous nanometric nature of nanosponges enables the drug molecules to orient themselves in inclusion as well as interact in a non-inclusion fashion, which offers higher drug loading when compared to their respective parent cyclodextrin molecules. Nanosponges solubilize poorly water-soluble drugs and provides prolonged release as well as improves the drug bioavailability by modifying the pharmacokinetic parameters of active constituents. Nanosponges can load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavity and external hydrophilic branching, thereby offering unparalleled flexibility 16. Nanospongespossess a three-dimensional network or scaffold. [25-29]

Components of Nanoemulsion:

Following are Main components of Nanoemulsions.[2-3]

Table No. 1: Components of Nanoemulsion

Sr. No.	Component	Examples
1.	Oils	Castor oil, Corn oil, Coconut oil, Evening primrose oil, linseed oil, Mineral oil, olive oil, peanut oil
2.	Emulgent	Natural lecithins from plant or animal source, phospholipids, castor oil Derivatives, polysorbates, sterylamine
3.	Surfactant	Polysorbate20, Polysorbate80, Polyoxy 60, castor oil, Sorbitan monooleate, PEG300, Caprylic glyceride
4.	Co- Surfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer
5.	Tonicity modifiers	Glycerol, Sorbitol, and xylitol
6.	Additives	Lower alcohol (ethanol), propylene glycol, 1, 3-butylenes glycol, sugars such as butylene
7.	Antioxidants	Ascorbic acid and tocopherol

Types of Nanoemulsions:

There are three types of nanoemulsion:

1. Oil in water Nanoemulsions wherein oil droplets are dispersed in the continuous aqueous phase;[5]

2. Water in oil Nanoemulsions wherein water droplets are dispersed in the continuous oil phase;[5]

3. Bi-continuous Nanoemulsions wherein microdomains of oil and water are interspersed within the system.[5]

Advantages:

- Nanoemulsions are thermodynamically and kinetically stable thus preventing flocculation, aggregation, creaming, and coalescence.[3]
- Increases the rate of absorption.[3]
- Helps in solubilizing lipophilic drug.[3]
- Provides aqueous dosage form for water-insoluble drugs.[3]
- Increases bioavailability.[4]
- Various routes like tropical, oral and intravenous can be used to deliver the product.[4]
- Rapid and efficient penetration of the drug moiety.[3]
- Helpful in taste masking.[3]
- Liquid dosage form increases patient compliance.[3]
- Rapid and efficient penetration of the drug moiety.[3]

Disadvantages:

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.[4]

2. Its stability is affected by temperature and pH.[4]

3. Instability can be caused due to Oswald ripening effect.[4]

4. Expensive process due to size reduction of droplets.[3]

Methods of preparation of nanoemulsions:

Methods used for the preparation of nanoemulsion are following:

1. Solvent Evaporation Technique: This technique involves preparing a solution of drug followed by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.[5]

2. Phase inversion method: In this method, fine dispersion is obtained by the use of chemical energy resulting from phase transitions produced by the emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping temperature constant or vice versa.[6]

3. Sonication Method: In this technique, the droplet size of the usual emulsion is compact with the help of the sonication mechanism. Only fewer amounts of batches of nanoemulsion can be produced by this method.[7]

4. Hydrogel Method: It is similar to the solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevent crystal growth and Ostwald ripening.[30]

5. High-Pressure Homogenization:

The preparation of nanoemulsions requires high- pressure homogenization. This technique makes use of high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1nm). The dispersion of two liquids (oily phase 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. The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids. This technique has great efficiency, the only disadvantage being high energy consumption and an increase in temperature of the emulsion during processing.[31]

6. Microfluidization Microfluidization: is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000psi), and it forces the product through the interaction chamber, which consists of small channels called,, microchannels". The product flows through the microchannels on to an impingement area resulting in fine particles of the submicron size range. The two solutions (aqueous phase and oily phase) are combined and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is inserted into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until the desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion. The premixed emulsion is circulated through the microfluidizer repeatedly until the required droplet size is achieved.[31]

Characterization of Nanoemulsion:

1. Zeta potential: Zeta potential is measured by an instrument known as Zeta potential. It is used to measure the charge on the surface of the droplet in nanoemulsion. Emulsifiers not only act as a mechanical barrier but also through the formation of surface charges. Zeta potential can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more negative zeta potential, the greater the net charge of droplets, and the more stable the emulsion is. Zeta potential values lower than -30 mV generally indicate a high degree of physical stability. Malvern Zeta sizer is based on dynamic light scattering and measures Zeta potential.[8]

2. Dye Solubilization: A water-soluble dye is solubilized within the aqueous phase of the W/O globule but is dispersible in the O/W globule. An oil-soluble dye is solubilized within the oil phase of the O/W globule but is dispersible in the W/O globule.[9]

3. Conductance Measurement: O/W Nanoemulsion where the external phase is water, are highly conducting whereas W/O is not, since water is the internal or dispersal phase. To determine the nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful. A sharp increase in conductivity in certain W/O Nanoemulsion systems was observed at low volume fractions and such behavior was interpreted as an indication of a "percolative behavior" or exchange of ions between droplets before the formation of bicontinuous structures. Dielectric measurements are a powerful means of probing both structural and dynamic features of Nanoemulsion systems.[12]

4. Particle Size Analysis: Generally in the case of nanoemulsion dynamic light scattering (DLS) method is used for the measurement of particle size and their distribution.[12]

5. In-vitro drug release: The in vitro release studies of nanoemulsion containing drugs can be investigated through a semi-permeable membrane used in a dissolution apparatus. A glass cylindrical tube (2.5 cm in diameter and 6 cm in length) is attached instead of the basket and should tightly cover with the semi-permeable membrane. Drug loaded nanoemulsion is placed in the cylindrical tube at the semi-permeable membrane surface. The cylindrical tube should dip in 100 ml buffer maintaining the pH to allow the establishment of the sink conditions and to sustain permanent solubilization. The release study can be carried out for 24 hrs. at 32ºC.The stirring shaft should rotate at speed of 100 r.p.m. At predetermined time intervals (1, 2, 4, 6, 8, 12, 20, 24 hrs.) aliquots of one milliliter of the release medium are withdrawn and diluted then filtered for analysis and replaced with an equal volume of the buffer solution to maintain a constant volume. The absorbance of the collected samples can be measured by UV spectrometer.[16]

6. Durability Test: O/W Nanoemulsions are dilutable with water whereas W/O is not and undergo phase inversion into O/W Nanoemulsion.[17]

7. Polydispersity: The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 25˚C using a HeNe laser.[32]

8. Interfacial Tension: The formation and the properties of Nanoemulsion can be studied by measuring the interfacial tension. Ultra-low values of interfacial tension are correlated with phase behavior, particularly the existence of surfactant phase or middle-phase Nanoemulsions in equilibrium with aqueous and oil phases. The Spinning-drop apparatus can

be used to measure the ultra-low interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.[32]

Applications of Nanoemulsion:

1. Nanoemulsion in Food Nanoemulsions:

Nanoemulsion can be used in the food industry to design smart foods with ingredients that are otherwise difficult to incorporate due to low-water solubility; an example is a beta-carotene, a pigment responsible for color in vegetables like carrots possessing important health benefits. The possible application of nanoemulsions in improving the digestibility of food. The researchers showed that nanoemulsions prepared with curcumin in the oil phase allow for easier digestion than when the circumin.[10]

2. Nanoemulsion in Cosmetics:

The cosmetic formulation mainly faced the problem of poor absorption of drugs through skin layers. With the help of nanotechnology and nanoemulsion, this problem can be resolved, and the absorption of cosmetics in the skin is get stimulated due to smaller droplet size. Recently the importance of nanoemulsions has become increasing as good vehicles for the controlled delivery of cosmetics and the optimized dispersion of active ingredients in particular skin layers. Nanoemulsions are used for the transport of lipophilic drug and it also supports the skin penetration of active ingredients and thus increases their concentration in the skin.[11]

3. Oral Delivery Nanoemulsion: formulations offer many advantages over conventional oral formulation for oral administration including increased absorption, improved clinical potency, and decreased drug toxicity. Thus, Nanoemulsion proves to be ideal in delivering drugs such as steroids, hormones, diuretics, and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. Primaquine when incorporated into oral lipid nanoemulsion showed effective antimalarial activity against Plasmodium bergheii infection in mice at a 25% lower dose level as compared to the conventional oral dose. Lipidnanoemulsion of primaquine improved oral bioavailability by the liver with drug concentration higher by at least by 45% as compared with the puredrug.[12]

4. Nanoemulsions in cell culture technology: Nanoemulsions are a new method for the delivery of oil-soluble substances to human cell cultures. The system is based on a nanoemulsion that is stabilized by phospholipids. This nanoemulsion is transparent and can be passed through 0.1mm filters for sterilization. Nanoemulsions oil droplets are very easily taken up by the cells.[11]

5. Nanoemulsions in Cancer Therapy: Nanoemulsions can be used as a vehicle in cancer chemotherapy for prolonging the rate of drug release after intramuscular and intratumoral injection (W/O systems). It also enhances the transdermal drug delivery due to the increase in the transport of anti-cancer drugs via lymphatic permeation through the skin and it is also non-irritant system.[12]

6. Nanoemulsions in ocular and otic drug delivery: To increase the effectiveness of the drug, a dosage form should be chosen which increases the contact time of the drug in the eye. This may then increase bioavailability, reduce systemic absorption, and reduce the need for frequent administration leading to improved patient compliance. So, nanoemulsions have been developed to overcome such problems.[10]

7. In Biotechnology: Many enzymatic and biocatalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of pure apolar media causes the denaturation of biocatalysts.[11]

Table No. 2: Formulation of Nanoemulsion:[13-19]

Sr. No.	Title of Paper	Material	Method	Conclusion	Reference
1.	Formulation and evaluation of nanoemulsion for enhancing bioavailability of Itraconazole**.**	Traconazole Poloxamer 188, Tween 80, Capryol 90.	solvent displacement method.	From the above-obtained results and it was concluded that formulations prepared by the lipid were in nano range and can be formulated. The tests carried out reveals that the mean droplet size was in the nanometre range, with good uniformity of diameter.	14
2.	Rutin loaded nanoemulsion formulation for brain tumor targeting: *In-vitro*, *ex-vivo* permeation and *in-vitro* cytotoxicity assay	Rutin-polyphenolic, Ethyl oleate, Tween 80 (polysorbate 80) and polyethylene glycol 400, Acetonitrile (HPLC grade) and Methanol (HPLC Graded)	Simultaneous Emulsification technique	Rutin nanoemulsion and it did not show any toxicity and so were safe for intranasal delivery for brain targeting. In-vitro diffusion studies revealed that Rutin loaded nanoemulsion (RU-NE) had a significantly higher release.	15
3.	Optimization of Finasteride Nano-Emulsion Preparation Using Chemometric Approach	Finasteride is a lipophilic drug) and water-miscible solvent with or without a lipophilic surfactant (Span® 80), while the aqueous phase consisted of water with or without hydrophilic surfactant (Tween® 80).	spontaneous emulsification method	The Box-Behnken experimental design is a suitable tool for optimizing and testing the robustness of the method for preparing finasteride nano-emulsion.	
4.	Development and stability evaluation of astaxanthin nanoemulsion	Astareal 10FC grade (an oil extract containing 10% w/w of standardized astaxanthin) (lecithin (L-phosphatidylcholine, Tween 80 (polyoxyethylene (20) sorbitan monooleate)	Homogenization Method	this study confirmed that the droplet size and size distribution (PDI) of astaxanthin nanoemulsion were influenced by the homogenization pressure and number of cycles, as well as type and concentration of emulsifier blend	
5.	Formulation and	Quercetin is a	Spontaneous	QUR loaded NE for intranasal	

	Evaluation of Quercetin Nanoemulsions for Treatment of Brain Tumor via Intranasal pathway	poorly water-soluble anticancer drug, Oleic acid, Tween 80, surfactant, and Polyethylene glycol 400 was employed as co-surfactant.	Emulsification technique.	delivery is considered as a promising vehicle for its targeting to CNS to treat brain cancer.	
6.	Stability Testing of Beclomethasone Dipropionate Nanoemulsion	Beclomethasone dipropionate, eucalyptus oil, Tween-40, pleurol oleic, glycol, Brij-35, propanol, isopropyl alcohol, and ethanol.	spontaneous emulsification method.	The study demonstrates that the physical and chemical stability of BD is enhanced when it is formulated as a nanoemulsion.	
7.	Preparation and Characterizations of Chitosan/Citral Nanoemulsions and their Antimicrobial Activity	Citral oil, chitosan, sodium tripolyphosphate, sodium tripolyphosphate, surfactant,	ultrasonication	the prepared chitosan/citral nanoemulsions can be a cost-effective way to protect crops from microbial pathogens. Because such formulations contain bioactive products, the development of resistant pathogens	
8.	Effect of Surfactant and Oil Type on Size Droplets of Betacarotene-Bearing Nanoemulsions	Miglyol-812, beta carotene, octyl octanoate, corn oil, Nonionic polysorbate surfactants tween 80, 21, 85. Other chemicals were analytical grade and procured from Sigma (Merck Chemical Co. Darmstadt, Germany)	Simultaneous Emulsification technique	nanoemulsion. Also, the droplet size of nanoemulsion was affected by the surfactant concentration, and there was SER=17.5% as an optimum surfactant concentration. In nanoemulsion produced using nonionic surfactant (tween 80) and 812 Mygliol (oil carrier phase) initially by an increment of the concentration up to SOR =175% and SER = 17.5%, the droplet size was decreased but after passing a special value, by increasing the surfactant concentration the average e droplet diameter was increased. Optimal nanoemulsion had high stability during 90 days of storage.	

Patent reports

Table No. 3: Examples of patent report on nanoemulsions

Title	Publication number	Publication date	Applicant
An aqueous photoprotective composition comprising hydrophilic metal oxide nano pigments and a vinylpyrrolidone homopolymer	EP1768749B1	15-10-2008	Loreal SA
Cosmetic pigment composition containing gold or silver nano-particles	US 20090022765A1	22-01-2009	Korea Research Institute of Bioscience and Biotechnology
Zeolite based UV absorbing and sunscreen compositions	US20050276761A1	15-12-2005	Gupta Shyam K
Skin whitening methods and compositions based on zeoliteâ€“active oxygen donor complexes	US20070166339A1	19-07-2007	BIODERM Research
Cosmetic composition containing retinol stabilized by porous polymer beads and nanoemulsion	US 20130095157A1	18-04-2013	Act Co Ltd
Nano-emulsion and cosmetic product compounded therewith	JP 2008127327A	05-06-2008	Ands Corporation
Healthy collagen cosmetic	JP 2005206567A	04-08-2005	Iwamoto Shigemi
Nanoemulsion comprising metabolites of ginseng saponin and a skin-care composition for anti-aging containing the same	EP 1327434A1	16-07-2003	Pacific Corp

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