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NANOEMULSION: A REVIEW

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ABSTRACT

Nanoemulsions are submicron sized emulsions which 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 a 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 systemic 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) type of emulsions with the average droplet size ranging from 5nm to 100 nm. The focus of this review article is on nanoemulsion and its current applications in various pharmaceutical fields. the aim of this review is focused on nanoemulsion advantages, disadvantages, various methods of preparation, characterization techniques and the various applications.

KEYWORDS: Nanoemulsion. drug delivery. flocculation. surfactant.

INTRODUCTION[1, 2]

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 determine 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 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 phase2-5.

Types of Nanoemulsions

There are three types of nanoemulsion

1. Oil in water Nanoemulsions wherein oil droplets are dispersed in the continuos aqueous phase;
2. Water in oil Nanoemulsions wherein water droplets are dispersed in the continuous oil phase;
3. Bi-continuous Nanoemulsions wherein microdomains of oil and water are interdispersed within the system.

Advantages of Nanoemulsions[3]

1. Nanoemulsions are thermodynamically and kinetically stable thus preventing flocculation, aggregation, creaming and coalescence.
2. Increases the rate of absorption.
3. Helps in solublizing lipophilic drug.
4. Provides aqueous dosage form for water insoluble drugs.
5. Increases bioavailability.
6. Various routes like tropical, oral and intravenous can be used to deliver the product.
7. Rapid and efficient penetration of the drug moiety. 8. Helpful in taste masking.
8. Liquid dosage form increases patient compliance.
9. Rapid and efficient penetration of the drug moiety.

Disadvantages of Nanoemulsions[4]

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
2. Its stability is affected by temperature and pH.
3. Instability can be caused due to Oswald ripening effect.
4. Expensive process due to size reduction of droplets.

Components of Nanoemulsion[5]

Following are Main components of Nanoemulsions

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 lecithin 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

Methods of preparation of nanoemulsions[6,7]

Method used for the preparation of nanoemulsion are following.

1. 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 increase in temperature of emulsion during processing.

2. Sonication Method

In this technique, the droplet size of usual emulsion is compact with the help of sonication mechanism. Only fewer amounts of batches of nanoemulsion can be produced by this method.

3. 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 micro channels. The product flows through the micro channels on to an impingement area resulting in fine particles of submicron size range. The two solutions (aqueous phase and oily phase) are combined together 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 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 microfludizer repeatedly until required droplet size is achieved.

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

B. 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.

C. Hydrogel Method: It is similar to 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.

Characterization of Nanoemulsion[8,9]

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 droplet in nanoemulsion. Emulsifiers not only act as a mechanical barrier but also through formation of surface charges. Zeta potential can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more negative zeta potential, greater the net charge of droplets and 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.

2. 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.

3. Conductance Measurement
O/W Nanoemulsion where the external phase is water, are highly conducting whereas W/O are 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 behaviour was interpreted as an indication of a „percolative behaviour" 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.

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

5. In-vitro drug release: The in vitro release studies of nanoemulsion containing drug can be investigated through 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 32℃.Tthe 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 millilitre of the release medium is withdrawn and diluted then filtered for analysis and replaced with equal volume of the buffer solution to maintain a constant volume. The absorbance of the collected samples can be measured by UV spectrometer.

6. Dilutability Test
O/W Nanoemulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nanoemulsion.

7. Polydispersity
The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 25oC using a HeNe laser.

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 behaviour, particularly the existence of surfactant phase or middle-phase Nanoemulsions in equilibrium with aqueous and oil phases. 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.

Applications of Nanoemulsion[10,11,12]
1. Nanoemulsion in Food Nanoemulsions
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 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 circumin in the oil phase allow for easier digestion than when the circumin.

2. Nanoemulsion in Cosmetics
The cosmetic formulation mainly faced problem of poor absorption of drugs through skin layers. With the help of nanotechnology and nanoemulsion, this problem can be resolve and absorption of cosmetic in skin is get stimulated due smaller droplet size. Recently the importance of nanoemulsions has become increasing as good vehicles for the controlled delivery of cosmetics and for 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.

2.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 of drugssuch as steroids, hormones, diuretic 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 berghei infection in mice at a 25% lower dose level as compared to conventional oral dose. Lipid nanoemulsion of primaquine improved oral bioavailability by the liver with drug concentration higher by at least by 45% as compared with the pure drug.

3. Nanoemulsions in cell culture technology
Nanoemulsions are a new method for the delivery of oilsoluble 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.

4. Nanoemulsions in Cancer Therapy

Nanoemulsions can be used as 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 increase in the transport of anti-cancer drugs via lymphatic permeation through the skin and it is also non-irritant system.

5.Nanoemulsions in ocular and otic drug delivery

In order 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 the 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.

6. **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 a polar media causes the denaturation of biocatalysts.

Formulation of Nanoemulsion[13 -19]

Sr.no	Title of Paper	Material	Method	Conclusion
1.	Formulation and evaluation of nanoemulsion for enhance bioavilability 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
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	Rutinnanoemulsion and it did not show any toxicity and so were safe forintranasal delivery for brain targeting. In-vitro diffusion studies revealed that Rutin loaded nanoemulsion (RU-NE) had a significantly higher release.
3.	Optimization of Finasteride Nano-Emulsion Preparation Using Chemometric Approach	Finasteride as a lipophilic drug) and water–miscible solvent with or without lipophilic surfactant (Span® 80), while the aqueous phase consisted of water with or without hydrophilic surfactant (Tween® 80).	Simultaneous Emulsification technique	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 Evaluation of Quercetin Nanoemulsions for Treatment of Brain Tumor via Intranasal pathway	Quercetin is a poorly water solubleanticancer drug,Oleic acid, Tween 80, surfactant and Polyethylene glycol 400 was employed as co-surfactant.	Spontaneous Emulsification technique.	QUR loaded NE for intranasal delivery are considered as promising vehicle for its targeting to CNS to treat the 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	Citral oil, chitosan, sodium tripolyphosphate, sodium tripolyphosphate, surfactant,	Ultrasonication	the prepared chitosan/citralanoemulsions can be a cost-effective way to protect crops from microbial pathogens. Because such

	Nanoemulsions and their Antimicrobial Activity			formulations contain bioactive products, the development of resistant pathogens
8	Effect of Surfactant and Oil Type on Size Droplets of Betacarotene-Bearing Nanoemulsions	Miglyol-8,beta carotene,octyl octanoate, corn oil, . Nonionic poly sorbate surfactants tween 80, 21, 85. Other chemicals were analytical grade and procured from Sigma (Merck Chemical Co. Darmstadt, Germany)	Simultaneous Emulsification technique	nanoemulsion.Also, 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 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 droplet diameter was increased. Optimal nanoemulsion had a high stability during 90 days .

REFERENCE

1. Kreilgaard, M; Pedersen, EJ and Jaroszewski, JW, "NMR characterization and transdermal drug delivery potential of microemulsion systems", J Control Release, 2000; 69: 421-433.
2. Gasco, MR; Gallarate, M and Pattarino, F, "In-Vitro permeation of azelaic acid from viscosized microemulsions", Int J Pharm, 1991; 69: 193-196.
3. Solans C, Esquena J, Forgiarini A, Morales D, Uson N, Izquierdo P., et al. Nanoemulsions: formation and properties.Surfactants in solution: fundamentals and applications, Surfactant Science Series,edited by : D. Shah, B. Moudgil, K.L. Mittal .Marcel Dekker, New York, 2002; 525–554.
4. Bhatt P, Madhav S. A detailed review on nanoemulsion drug delivery system. International Journal of Pharmaceutical Science and Research, 2011; 2(10): 248-489.
5. Tadros TF. Formation and stability of nanoemulsions. Adv Colloid Inter face Sci, 2004;108: 303-318.
6. KhHussanR.Nanoemulsion as a Novel Transdermal Drug Delivery System. International Journal of Pharmaceutical Sciences and Research, 2011; 2(8): 1938-1946.
7. Thakur A, Walia MK, Kumar SLH. Nanoemulsion in enhancement of bioavailability of poorly soluble drugs: A review. An International Research Journal, 2013; 4(1): 15-25.
8. Pershing L K, Parry G E, Lambert L D; Disparity of in vitro and in vivo oleic acidenhanced b-estradiol percutaneous absorption across human skin. Pharm. Res, 1993; 10: 1745– 1750.
9. Tanojo H, Junginger H E, Boddé H E: In-vivo human skin permeability enhancement by oleic acid: transepidermal water loss and Fourier-transform infrared spectroscopy studies. Journal of Control Release, 1997; 47: 31–39.
10. Tamilvanan S. Submicron emulsions as a carrier for topical (ocular and percutaneous)and nasal drug delivery.
11. 11.D Subhashis, J Satayanarayana, VK Gampa. Nanoemulsion-a method to improve the solubility of lipophilic drugs. pharmanest- Int. J. Adv. Pharm. Sci, 2011; 2(2-3): 72-83.
12. Kreilgaard M, Kemme MJB, Burggraaf J, Schoemaker RC, Cohen AF. Influence of a microemulsion vehicle on cutaneous bioequivalence of a lipophilic model drug assessed by microdialysis and pharmacodynamics. Pharm Res, 2001; 18: 593Y599.
13. JyotsanaSuyal , Ganesh Bhatt and Nardev Singh , formulation and evaluation of nanoemulsion for enhanced bioavailability of itraconazole, Int J Pharm Sci Res, 2018; 9(7): 2927-31.
14. Hitendramahajan, shamshadbeldar, Rutin loaded nanoemulsion formulation for brain tumor targeting: In vitro, ex vivo permeation and in vitro cytotoxicity assay, Indian Journal of Novel Drug Delivery, Apr-Jun, 2017; 9(2): 96-106.
15. Soheila Honary ,Pouneh Ebrahimi and MahshidNikbakht, Optimization of Finasteride Nano-Emulsion Preparation Using Chemometric Approach, Tropical Journal of Pharmaceutical Research, August 2013; 12(4): 457-460.
16. mmrmeormohdaffandia, T juliantoa, ABA majeeda, development and stability evaluation of astaxanthin nanoemulsion, Asian J Pharm Clin Res, 2011; 4(1): 142-148.
17. Sagar Kishor Savale, Formulation and Evaluation of Quercetin Nanoemulsions for Treatment of Brain Tumor via Intranasal pathway,Asian Journal of Biomaterial Research, 2017; 3(6): 28-32.
18. Mohammad Sarfaraz Alam, Mohammad Sajid Ali, Mohammad IntakhabAlam,Stability Testing of Beclomethasone Dipropionate Nanoemulsion, Tropical Journal of Pharmaceutical Research, January 2015; 14(1): 15-20.
19. Fardin Hasani, AkramPezeshki and Hamed Hamishehkar, Effect of Surfactant and Oil Type on Size Droplets of Betacarotene-Bearing Nanoemulsions, Int.J.Curr. Microbiol. App. Sci, 2015; 4(9): 146-155.