International Journal of Pharmaceutical Sciences and Drug Analysis

E-ISSN: 2788-9254
P-ISSN: 2788-9246
IJPSDA 2022; 2(2): 38-43
Received: 15-04-2022
Accepted: 19-06-2022

Rajia Sultana Nijhu
Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka, Bangladesh

Ambia Khatun
Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka, Bangladesh

Md. Abdul Mannan
Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka, Bangladesh

Correspondence
Md. Abdul Mannan
Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka, Bangladesh

Nanoemulsions: A propelled method of medication

Rajia Sultana Nijhu, Ambia Khatun and Md. Abdul Mannan

Abstract
Nanoemulsions have recently generated a lot of attention in a wide variety of sectors, because of their unique physicochemical and physiological features. Nanoemulsions can be translucent, have good droplet aggregation and creaming stability, have new textural qualities, and have great bioavailability due to the tiny size of the droplets. These are thermodynamically stable isotropic systems in which an emulsifying agent, such as surfactant and co-surfactant, is used to combine two immiscible liquids into a single phase. Nanoemulsion droplets are generally 20–200 nanometers in size. The size and form of particles distributed in the continuous phase are the fundamental differences between emulsion and nanoemulsion. Overall, all nanoemulsion formulations are efficacious, safe, and have a higher bioavailability. Nanoemulsions are projected to be the subject of more study and development in the future. This review focuses on providing a fundamental understanding of nanoemulsion formulation, production process, characterisation techniques, assessment criteria, and numerous applications.

Keywords: Nanoemulsion, microfludization, water in oil (w/o), oil in water (o/w)

Introduction
Nanotechnology has quickly risen to become one of the most promising and appealing study disciplines in the last two decades. Many functional compounds solubility and bioavailability might be considerably improved with this method. Nanotechnology is described by the British Standard Institution as the design, characterisation, manufacture, and use of structures, devices, and systems at the nanoscale (Bawa *et al*., 2005) [1]. Nanoemulsions are a non-equilibrium, heterogeneous system made up of two immiscible liquids, one of which is distributed as droplets in the other. (Huabing *et al*., 2011) [2]. A thermodynamically stable isotropically transparent dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial coating of surfactant molecules is referred to as a "Nanoemulsion."
It is defined as oil-in-water (o/w) emulsion with mean droplet diameters ranging from 50 to 1000 nm. Sub-micron emulsion and mini-emulsion are terms that are used interchangeably when the average droplet size is between 100 and 500 nm (Sangwan *et al*., 2014) [3]. Nanoemulsions are a type of dispersed particle employed in pharmaceutical and biological aids and vehicles with a bright future in cosmetics, diagnostics, drug therapies, and biotechnologies (Ochekpe *et al*., 2009) [4].
Nanoemulsions are increasingly being utilized to administer vaccines, DNA-encoded drugs, antibiotics, cosmetics, and topical treatments via a variety of routes, including oral, pulmonary, intranasal, ophthalmic, and transdermal (Thakur *et al*., 2012) [5]. Nanoemulsions are emulsified oil and water systems that are used to deliver drugs (Ravi *et al*., 2011) [6]. Pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions, suspension, cachets, troches, lozenges, nebulizers, and a variety of other conventional delivery mechanisms were among the ways employed. Drugs produced from plant extracts are used in several of these delivery systems (Paolino *et al*., 2006) [7].

Classification of Nanoemulsions
Depending on the composition, nanoemulsions are most likely to form:
1. Nanoemulsions of oil in water, in which oil droplets are scattered in a continuous aqueous phase.
2. Water in oil nanoemulsions, which have water droplets scattered throughout the continuous oil phase.
3. Bi-continuous nanoemulsions, in which oil and water microdomains are intermixed inside the system.

A proper mix of surfactants and co-surfactants stabilizes the interface in all three forms of nanoemulsions. The appearance of emulsions and nanoemulsions differs significantly; emulsions are foggy, but nanoemulsions are transparent or translucent (Kriwet *et al*., 1995) [8].

Applications

Nanoemulsions have a higher surface area and free energy, making them an efficient mode of transportation (Daniel *et al*., 2015) [9]. It enables for adequate absorption of oil-soluble additives in cell culture technologies, allowing for improved cell growth and toxicity testing of oil-soluble pharmaceuticals (Bhosale *et al*., 2014) [10]. Nanoemulsions have a tiny droplet size, which allows for better absorption (Jaiswal *et al*., 2015) [11].

Topical Delivery

Topical medication delivery has various advantages over other approaches, one of which being the avoidance of the drug's hepatic first-pass metabolism and associated adverse consequences. Another advantage is that the medicine can be delivered directly to the damaged region of the skin or eyes. The nanoemulsion can attain a degree of antibacterial activity on the skin that was previously only possible with systemic antibiotics. The nanoemulsion is effective against bacteria (such as E. coli and S. aureus) as well as fungus (e.g. Candida, Dermatophytes) (Kemken *et al*., 1992) [12].

Ocular Delivery

Drugs are mostly used topically in the treatment of eye disorders. O/W nanoemulsions have been studied for ocular delivery, as well as for dissolving poorly soluble medicines, increasing absorption, and achieving a longer release profile (Kreilgaard *et al*., 2001) [13].

Components of Nanoemulsion

There are three major components in a nanoemulsion. Oil, surfactant/co-surfactant, and aqueous phase are the three types (Singh *et al*., 2011) [14].

Oil

The drug's solubility in the oil phase is a significant criteria for choosing oils. The capacity of the nanoemulsion to preserve the drug in solubilized state is highly impacted by the drug's solubility in the oil phase, which is especially essential in the case of oral formulation development. There is a danger of precipitation if the surfactant or cosurfactant contributes to medication solubilization, because dilution of the nanoemulsion in the gastrointestinal system reduces the surfactant or cosurfactant's solvent capacity.

Surfactant/Co-surfactant

There are three types of surfactants used to stabilize systems: anionic, cationic, and non-ionic. Non-ionic surfactants are less hazardous than their ionic counterparts, and their CMCs are often lower.

To generate nanoemulsion systems with low surfactant concentrations, co-surfactant is added. Cosurfactants with short to medium chain length alcohols (C3-C8) are often used to lower interfacial tension and promote interface fluidity. They also boost the hydrocarbon tail's motility, allowing oil to penetrate deeper into the area. Transcutol p, glycerin, propylene glycol, ethanol, and propanol are among examples.

Aqueous phase

The composition of the aqueous phase can impact the size of the droplets and the stability of the nanoemulsion. During nanoemulsion preparation, pH and the presence of electrolytes in the aqueous phase should be carefully considered.

Factors affecting formulation of nanoemulsion

1. To avoid Oswald ripening, the dispersed phase must have a composition that is extremely insoluble in the dispersed medium.
2. The surfactant is an essential component of a nanoemulsion. They should not form liquid crystalline lyotropic microemulsion' phases. The phases that are employed with the co-surfactant are made up of short chain alkanes, alcohols, water, and surfactants (Reza *et al*., 2011) [16].
3. The presence of excessive surfactants allows fresh nanoscale surface area to be covered fast during emulsification, preventing induced coalescence.
4. Extreme share must be used to shatter microscalegloules to nanoscale by raising the stress level over the droplets' laplace pressure (pressure of 10-100 atm) (Mangale *et al*., 2015) [15].

Materials and methods

Materials

Oils, surfactants, and co-surfactants, as well as an aqueous phase, are used to make nanoemulsions (Adnan *et al*., 2009) [17].

Captex 355, Captex 8000, Witepsol, myritol 318, Isopropyl myristate, Capryol 90, Sefsol-218, triacetin, castor oil, olive oil, and other oils are utilized in the creation of nanoemulsions (Lawrence *et al*., 2000) [18].

The surfactants may include capryol 90, gelucire 44/14, 50/13, cremophor RH 40, imwitor 191, 742, 780 k, 928, 988, Labrafil CS, M, 2125 CS, Lauroglycol 90, PEG MW > 4000, PlurolOleique CC 497, Poloxamer 124 and 188, Softigen 701, 767, Labrasol, Cremophor EL, Tween 20, Tween 60, and Tween 80, etc. (Kawakami *et al*., 2002) [19].

Co-surfactants used in nanoemulsions include Transcutol P, glycerin, ethyleneglycol, ethanol, propanol, ethanol, isopropyl alcohol, n-butanol, PEG 400, Carbitol, and propylene glycol (Tenjarla *et al*., 1999; Attwood *et al*., 1994) [20, 21].

Methods

The active medicine, additive, and emulsifier are all part of the nanoemulsion formula. High-energy emulsification and low-energy emulsification are two ways for producing nanoemulsions. High-energy stirring, ultrasonic emulsification, high-pressure homogenization, microfluidization, and membrane emulsification are some of the techniques used in high-energy emulsification (Tiwari and Amiji, 2006; Perdiguer *et al*., 1997) [22, 23]. Phase inversion temperature, emulsion inversion point, and spontaneous emulsification are all low-energy emulsification methods. It is feasible to create reverse nanoemulsion in a very viscous solution using a combination technique that comprises both high-energy and low-energy emulsification (Ahuja *et al*., 2008) [24].

High Pressure Homogenization

Nanoemulsion preparation necessitates the use of a high-

pressure homogenizer. This method creates nanoemulsions with a particle size of 10-100nm. The (oily and aqueous phase) are dispersed by pushing their combination through a tiny input orifice at a high pressure (500 to 5000 psi), causing strong turbulence and hydraulic shear, resulting in very thin emulsion particles as illustrated in Figure. A monomolecular layer of phospholipids separates the liquid, lipophilic core from the surrounding aqueous phase in the particles that are generated.

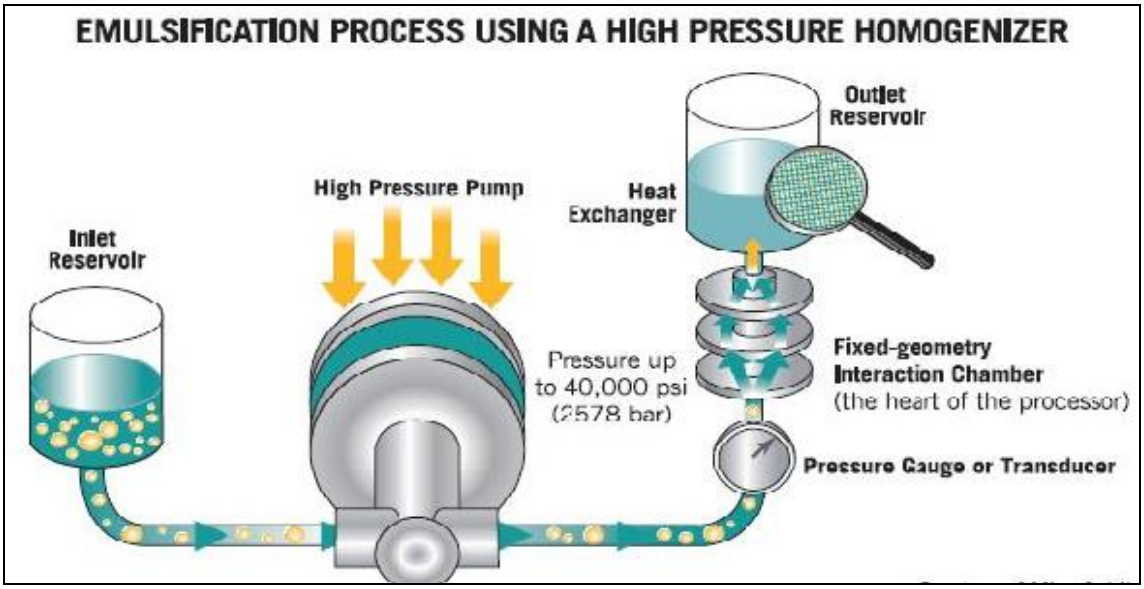

Fig 1: High pressure homogenizer

Following process factors should be explored in order to reach the optimal formulation:

- Homogenization and Its Consequences It should be between 100 and 150 bars of pressure. The particle size achieved decreases as the pressure increases.
- Number of Homogenization Cycles: The more homogenization cycles there are, the smaller the particle size. Three, four, or ten cycles are completed. After each cycle, the number of cycles is calculated using the drug's polydispersity index (Reza *et al*., 2011) [16].

Microfluidization

Microfluidization is a mixing process that employs the use of a microfluidizer device. The product is forced into the interaction chamber, which is made up of small channels termed "micro channels," by a high-pressure positive displacement pump (500 to 20000psi). The product runs through the micro channels and impinges on the impingement region, resulting in tiny sub-micron particles. To make a coarse emulsion, the two solutions (aqueous phase and oily phase) are mixed and homogenized in an inline homogenizer. The coarse emulsion is placed in a microfluidizer and treated further to produce a stable nanoemulsion. The coarse emulsion is cycled through the interaction chamber microfluidizer many times until the required particle size is attained. The bulk emulsion is then filtered under nitrogen to remove large droplets and produce a homogenous nanoemulsion. The microfludizer constantly circulates the premixed emulsion until the required droplet size is achieved (Gupta *et al*., 2010) [25].

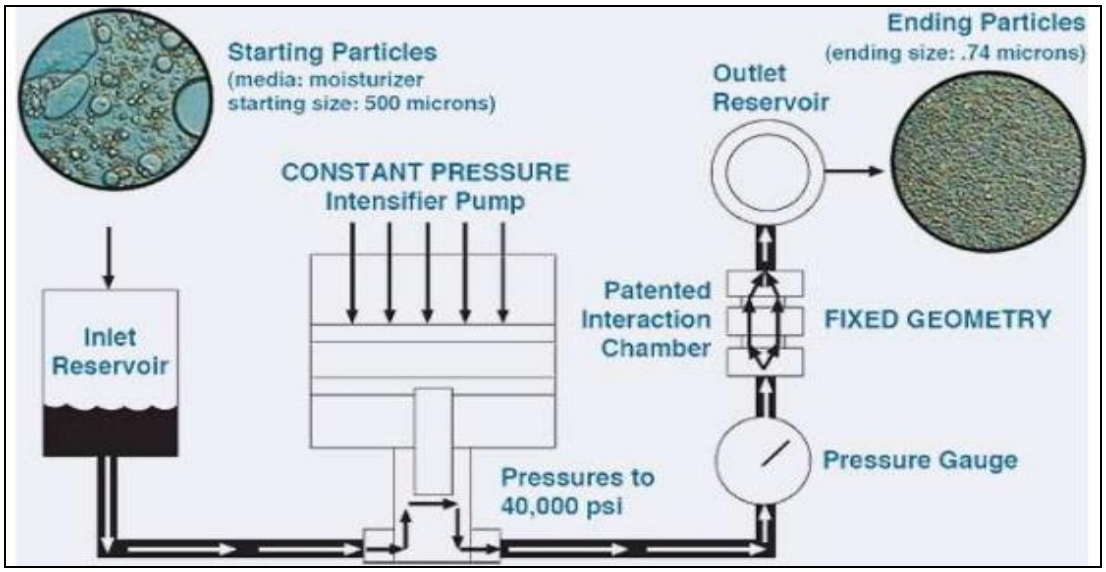

Fig 2: Microfluidiztion

Ultrasonication

By lowering the globule size, ultrasonic sound frequency may be employed to make nanoemulsions. Another option is to use a constant amplitude sonotrode at system pressures higher than the ambient value. Raising the external pressure inside an ultrasonic field reduces the cavitation threshold, resulting in fewer bubbles forming, as is well known. Increasing the external pressure, on the other hand, increases the cavitation bubbles' collapse pressure. This means that when cavitation occurs, the bubbles collapse more quickly and violently than when the pressure is at atmospheric levels. Changes in navigational intensity may be directly connected to changes in power density since cavitation is the most important source of power dissipation in a low frequency ultrasonic system. A water jacket is also employed in the system to maintain a comfortable temperature. (Kim *et al*., 1992) [26].

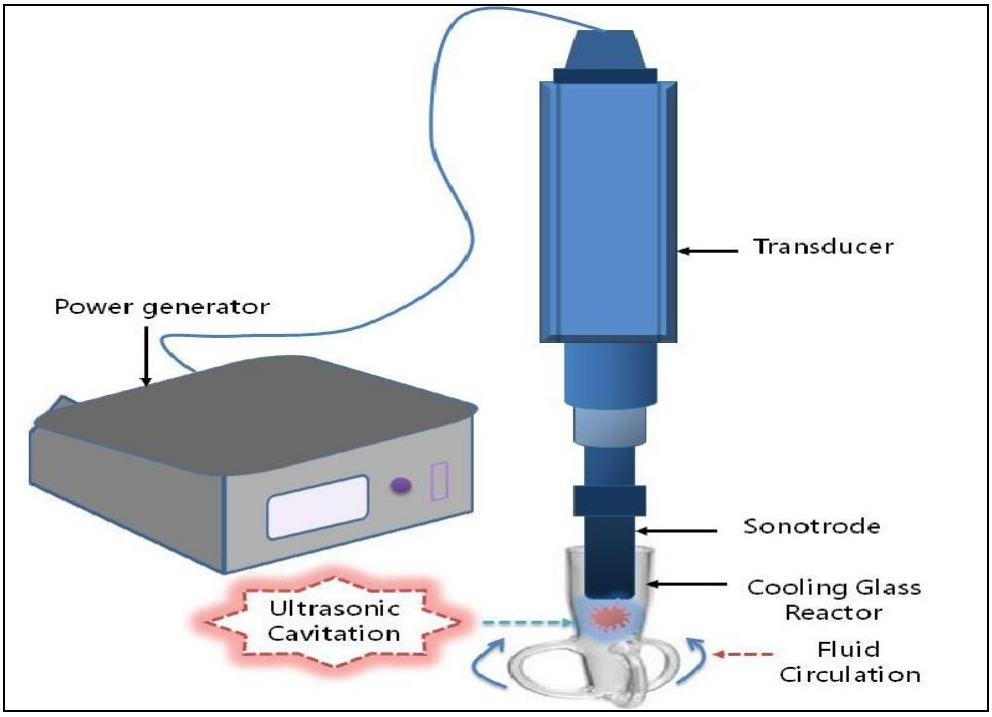

Fig 3: Ultrasonication

Phase inversion method

Chemical energy derived from phase changes generated by the emulsification pathway is employed to achieve fine dispersion in this procedure. Change the emulsion composition while keeping the temperature constant, or vice versa, to generate a phase transition (Kim *et al*., 1992) [26].

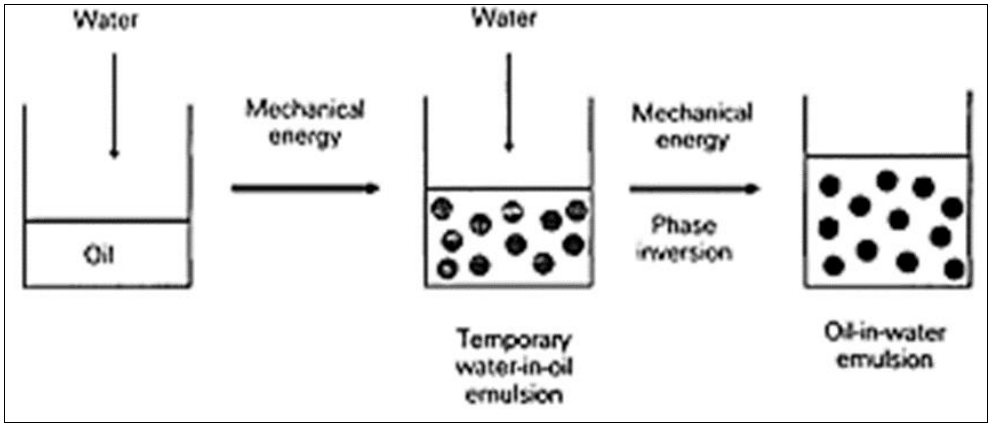

Fig 4: Phase inversion method

Spontaneous emulsification

It consists of three basic steps: (i) preparation of a homogeneous organic solution containing oil and a lipophilic surfactant in a water miscible solvent and a hydrophilic surfactant, (ii) injection of the organic phase into the aqueous phase under magnetic stirring to produce an o/w emulsion, and (iii) removal of the water-miscible solvent by evaporation under reduced pressure (Kim *et al*., 1992) [26].

Solvent evaporation technique

This procedure entails making a drug solution and then emulsifying it in a liquid that isn't a solvent for the medication. Evaporation of the solvent causes the medication to precipitate. Using a high-speed stirrer, large shear forces may be created to regulate crystal formation and particle aggregation (Patel and Joshi, 2012) [27].

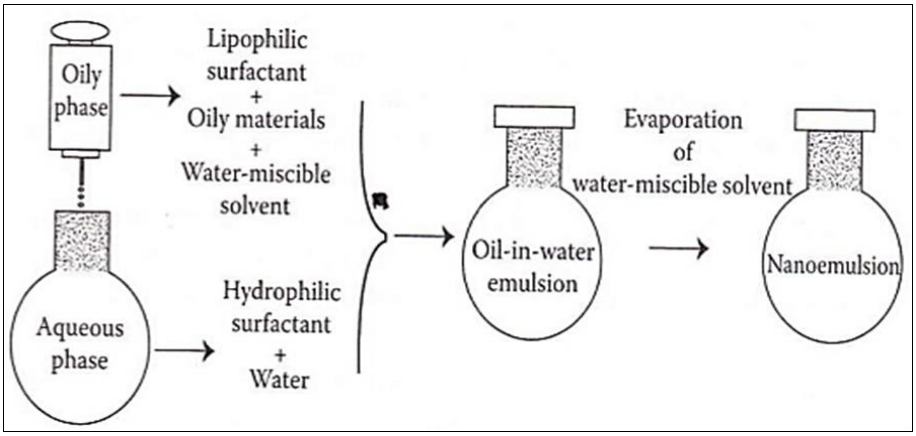

Fig 5: Solvent evaporation technique

Hydrogel Method

It works in the same way as the solvent evaporation technique. The drug solvent is miscible with the drug anti-solvent, which is the sole difference between the two procedures. Crystal growth and Ostwald ripening are prevented by increased shear stress (Mishra *et al*., 2011) [28].

Evaluation parameters of nanoemulsion

Droplet size

The diffusion method is used to measure the droplet size of nanoemulsions using a light-scattering particle size analyser counter, the LS 230. Correlation spectroscopy, which investigates the variation in light scattering owing to Brownian motion, is also used to quantify it. Transmission electron microscopy may also be used to examine the size of nanoemulsion droplets (Bouchemal *et al*., 2004a) [29].

Viscosity determination

A Brookfield-type rotational viscometer is used to test the viscosity of nanoemulsions at various shear rates and temperatures.

Dilution test

This kind may be identified by diluting a nanoemulsion with either oil or water. The test is predicated on the idea that a nanoemulsion may have additional continuous phase added to it without losing its stability. A w/o nanoemulsion may be diluted with oil, whereas an o/w nanoemulsion can be diluted with water.

Dye test

When a water-soluble dye is applied to an o/w nanoemulsion, the color is evenly taken up by the nanoemulsion. In contrast, if the emulsion is w/o type and the dye is water soluble, the emulsion only picks up the color in the dispersion phase, resulting in an emulsion that is not evenly colored. A microscopic study of the emulsion can disclose this right away.

Refractive index

The Abbes refractometer is used to determine the nanoemulsion's refractive index.

pH

A pH meter may be used to determine the pH of nanoemulsion.

Zeta potential

The Zeta PALS equipment is used to measure zeta potential. It's used to determine the charge on a droplet's surface in a nanoemulsion (Yilmez *et al*., 2005) [30].

Fluorescence test

When exposed to ultraviolet light, many oils glow. The whole field fluoresces when a w/o nanoemulsion is subjected to fluorescence light under a microscope. If the fluorescence is patchy, use an o/w nanoemulsion.

Percentage transmittance

A UV-visible spectrophotometer is used to determine the percentage transmittance of nanoemulsion.

Conductance measurement

A conductometer is used to test the conductivity of nanoemulsion. A pair of electrodes linked to a light and an electric source are dipped in an emulsion in this test. Water conducts current in an o/w emulsion, and the lamp is lit as a result of current passing between the electrodes. When the emulsion is w/o, the lamp does not light because the oil in the exterior phase does not conduct current.

Conclusion

Nanoemulsions have a number of advantages when it comes to drug delivery, and are thus gaining popularity as drug carriers for improving the delivery of active pharmaceutical ingredients. They are suitable to practically all delivery routes and hence show promise in a variety of sectors, including cosmetics, pharmaceuticals, and biotechnology. This innovative method might be used to overcome the poor absorption of some phytopharmaceuticals as well as their low miscibility with the lipids found in cell membrane linings. The most common use of nanoemulsion is to cover up the unpleasant taste of greasy liquids. The medications, which are sensitive to hydrolysis and oxidation, may also be protected by nanoemulsion. Nanoemulsions are now widely employed for the targeted administration of anticancer medicines, photo sensitizers, and therapeutic agents. Nanoemulsions can potentially extend the duration of a drug's activity. Overall, all nanoemulsion formulations are efficacious, safe, and have a higher bioavailability. Nanoemulsions are projected to be the subject of more study and development in the future.

References

1. Bawa R, Bawa TSR, Maebius SB, Flynn T, Wei C. Protecting new ideas and inventions in nanomedicine with patents. Nanomedicine: nanotechnology, biology, and medicine. 2005;1(2):150-158.
2. Huabing C, Chalermchai K, Xiangliang Y, Xueling C, Jinming G. Nanonization strategies for poorly water-soluble drugs. Drug Discovery Today. 2011;16(7-8):354-60.
3. Sangwan Y, Hooda T. Nanoemulsions: A Pharmaceutical Review. International J. of Pharma Professional Research. 2014;5(2):1031-1038.
4. Ochekpe NA,Olorunfemi PO,Ngwuluka NC. Nanotechnology and Drug Delivery Part 2: Nanostructures for Drug Delivery. Tropical J. of Pharmaceutical Research. 2009;8(3):275-287.
5. Thakur N, Garg G, Sharma P.K. and Kumar N. Nanoemulsions: A Review on Various Pharmaceutical Applications. Global J. of Pharmacology. 2012;6(3):222-225.
6. Ravi TPU, Padma T. Nanoemulsions for drug delivery through different routes. Res. Biotechnol. 2011;2(3):1-13.
7. Paolino D, Webster J. Encyclopedia of Medical Devices and Instrumentation. Drug delivery. John Wiley & Sons, 2006, 437-487.
8. Kriwet K, Müller-Goymann, CC. "Diclofenac release from phospho- lipid drug systems and permeation through excised human stratum corneum. Int J Pharm. 1995;125(2):231-242.
9. Daniel M, Fuzette A, Kanika B. Essential Oil Nanoemulsions and Food Applications. Advances in food technology and nutritional sciences. 2015;1(4):84-87.
10. Bhosale RR, Osmani RA, Ghodake PP, Shaikh SM, Chavan SR. Nanoemulsion: A Review on Novel Profusion in Advanced Drug Delivery. Indian J. of Pharmaceutical and Biological Research. 2014;2(1):122-127.
11. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. *3* Biotech. 2015;5(2):123-127.
12. Kemken J, Ziegler A, Muller BW. Influence of supersaturation on the pharmacodynamic effect of bupranolol after dermal administration using microemulsions as vehicle. Pharm Res. 1992;9(4):554-558.
13. 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(5):593-599.
14. Singh Y, Dr. Amreesh Chandra. Review article on Nanoemulsions. International J. of Pharmaceutical Sciences. 2011;3(3):1443-1450.
15. Mangale MR, Pathak SS, Mene HR, More BA. Nanoemulsion: As Pharmaceutical Overview. International J of Pharmaceutical Sciences, Review and Research. 2015;33(1):244-252.
16. Reza K. Nanoemulsion as a novel transdermal drug delivery system. International J. of Pharmaceutical Sciences and Research. 2011;2(8):1938-1946.
17. Adnan A, Mohammad R, Farhan JA, Zeenat I, Roop KK, Aqil M, *et al*. Nanoemulsion components screening and selection: a technical note. AAPS Pharm Sci Tech. 2009;10(1):69-76.
18. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv. Drug Deliv. Rev. 2000;45(1):89-121.
19. Kawakami K, Yoshikawa T, Moroto Y, Kanaoka E, Takahashi K, Nishihara Y, Masuda K. Microemulsion formulation for enhanced absorption of poorly soluble drugs. II. *In vivo* study. J. of Controlled. Release. 2002;81(1-2):75–82.
20. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. Crit. Rev. Ther. Drug Carrier Syst. 1999;16(5):461–521.
21. Attwood TK. Beck ME. Bleasby AJ. Parry-Smith DJ. A database of protein motif fingerprints. Nucleic Acids Res. 1994;22(17)**:**3590–3596.
22. Tiwari SB, Amiji MM. Nanoemulsion formulations for tumortargeted delivery. Nanotech Cancer Therapy. Taylor & Francis, 2006, 723-739.
23. Perdiguer AC. Dachs FJG. Carreras N. Valdivia. Nanoemulsion of the oil water type, useful as an ophthalmic vehicle and process for the preparation there of Assignee: Laboratorios Cusi, S.A. 1997.
24. Ahuja A, Ali J, Baboota S, Faisal MS, Shakeell F, Shafiq. Stability evaluation of Celecoxib nanoemulsion containing Tween 80. Thai J Pharm Sci 2008;32:4-9.
25. Gupta P. Novel Nanoemulsion - High Energy Emulsification Prepara-tion. Evaluation and Application. Pharmaceutical Nanotechnology the-Pharma Research. 2010;3:117-138.
26. Kim YH, Ghanem AH, Mahmoud H and Higuchi WI. Short chain alkanols as transport enhancers for lipophilic and polar/ionic permeants in hairless mouse skin: mechanism(s) of ac-tion. International Journal of Pharmaceutics.1992;80(1-3):17-31.
27. Patel and Joshi. An overview on nanoemulsion: a novel approach. International J. of Pharmaceutical Sciences and Research. 2012;3(12):4640-4650.
28. Mishra RK, Soni GC, Mishra RP. A review article: on nanoemulsion. World J. of Pharmacy and Pharmaceutical sciences. 2014;3(9):258-274.
29. Bouchemal K, Briancon S, Fessi H, Perrier E. Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization. International J. of Pharmaceutics. 2004a;280(1-2):241-251..
30. Yilmez E, Borchert HH. Design of a phytosphingosine containing, positively-charged nanoemulsion as a colloidal carrier system for dermal application of ceramides. European Journal of Pharmaceutics and Biopharmaceutics. 2005;60(1):91-98.