Chapter

The Nanoemulsion Technique, One of the Most Promising Strategies for Enhancing Drug Permeation through Transdermal Route

Muhammad Rehan Malik, Asif Nawaz and Wajiha Noor

Abstract

Nanoemulsions are colloidal particulate systems that have gained significant attention in pharmaceutical research due to their potential in enhancing drug permeation through transdermal routes. This chapter provides a comprehensive overview of nanoemulsions, including their definition, advantages over other dosage forms, components, methods of preparation, and applications, with a focus on multiple nanoemulsions. The advantages of nanoemulsions include increased absorption rate, reduced absorption variability, improved drug bioavailability, and efficient delivery of both hydrophilic and lipophilic drugs. Various components such as oil phase, surfactants, co-surfactants, aqueous phase, and co-solvents are discussed in detail, along with their roles in nanoemulsion formulation. Methods of nanoemulsion preparation, including high-pressure homogenization, ultrasonic emulsification, high-shear stirring, microfluidization, and membrane emulsification, are elaborated upon, highlighting their respective advantages and limitations. Additionally, applications of nanoemulsions in medicine, catalysis, and theranostics are explored, emphasizing the potential of multiple nanoemulsions in drug delivery systems. Overall, nanoemulsions offer a promising approach for improving drug delivery efficiency and enhancing therapeutic outcomes.

Keywords: nanoemulsion, multiple nanoemulsion, method of preparation, topical delivery cargo, biomedical applications

1. Introduction

1.1 Nanoemulsion

The nanoemulsion technique is one of the most promising strategies for enhancing drug permeation through transdermal route. Submicron emulsions, ultrafine emulsions, and miniemulsions are the term used for nanoemulsion. It may be defined as a system: A submicron sized colloidal particulate system, thermodynamically or

kinetically stable isotopically clear dispersions of an oil phase and water phase. The two immiscible liquids are stabilized by an interfacial film of a suitable surfactant and co-surfactant molecules to form a single phase.

A variety of surfactants with different properties that may be ionic or non-ionic have been used with such nanoemulsions. The most commonly used surfactants are sorbitan esters, polysorbates (nonionic surfactants), potassium laurate, sodium lauryl sulphate (anionic surfactants), quaternary ammonium halide (cationic surfactants) etc. The first nanoemulsions were the Oil/water type emulsions, and their droplet size varying from 50 to 1000 nm. The nanoemulsions may be: O/W (oil dispersed in aqueous phase), W/O (water dispersed in oil phase), and multiple emulsions (a type of nanoemulsion that contain both O/W and W/O emulsions in the same system). Both hydrophilic and lipophilic surfactants are used to stabilized such types of systems (i.e., multiple emulsions) simultaneously [1].

1.2 Advantages of nanoemulsions over other dosage forms

1. Increased absorption rate due to vary small droplet size of the nanoemulsion.
2. Reduced absorption variability.
3. In O/W nanoemulsions, protection against oxidation and hydrolysis.
4. Lipophilic drugs delivery after solubilization.
5. Aqueous dosage form for water insoluble drugs.
6. Improved bioavailability of the drugs.
7. Both lipophilic and hydrophilic drugs are incorporated in nanoemulsions.
8. Efficient delivery system for drugs to increase efficiency there by reducing total daily dose and side effects.
9. Nonirritating and non-toxic drug delivery vehicle for skin and mucous membrane.
10. Control release of the drug through nanoemulsion (liquid film) whose thickness, lipophilicity or hydrophilicity may also be controlled.

It not only improves existing emulsion systems, but it also opens up new possibilities for other drugs to be formulated more specifically.

According to the research, nanoemulsion formulations exhibit better cutaneous and transdermal drug transport capabilities with respect to *in-vitro* [2, 3] and *in-vivo* [4, 5] as compared to emulsions [6] and gels [7].

Although nanoemulsion can be used to deliver drugs to patient in no of ways but topical application of nanoemulsion is gaining attention. The mobility of the drug in the vehicle, the release of the drug from the vehicle, and the permeation of the drug into the skin are the three key factors that determine drug transdermal permeation.

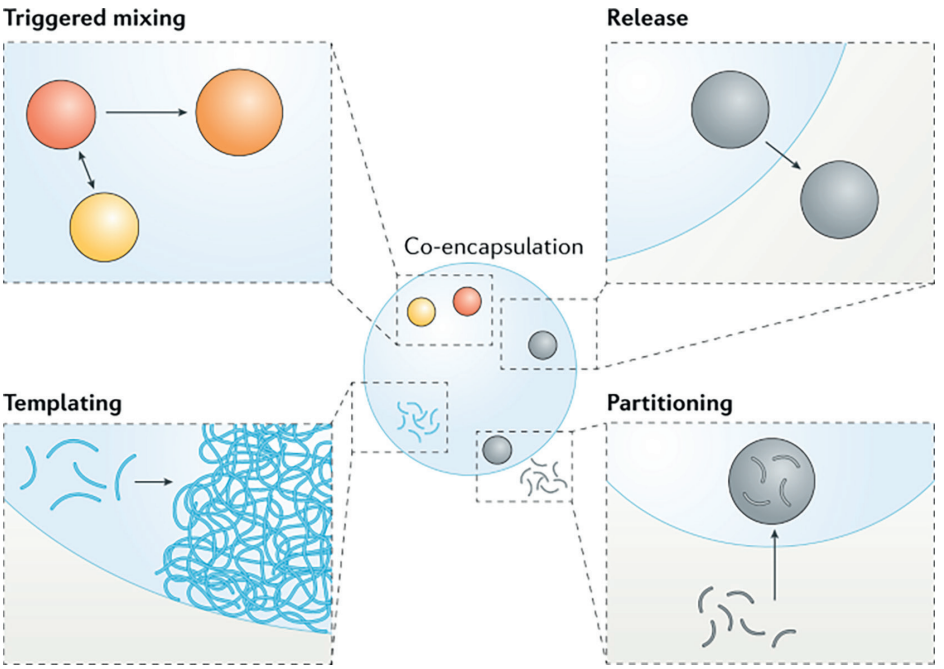

Figure 1.
Design features of multiple nanoemulsions [12].

1.3 Applications of multiple nanoemulsion

Nanoemulsions are used in a variety of fields, such as medicine [8, 9], catalysis [10], and theranostics [11]. Multiple nanoemulsions have distinct advantages for these applications, such as specified phases and internal compartments that can be used to encapsulate multiple cargos at the same time or serve as models for complex nanomaterials (**Figure 1**) Because of their unique structural features and small size, multiple nanoemulsions have significant potential for current nanoemulsion and multiple emulsion applications.

As compared to traditional nanocarriers, [13] optimized an O/W/O multiple nanoemulsion for dermal delivery of antiviral drug aciclovir., which showed efficient skin penetration and better physicochemical stability. Although hydrophilic drugs are more prone to degradation after oral administration, so multiple nanoemulsions can help improve bioavailability in this situation.

As a result, a low-energy method was established by [14] to incorporate hydrophilic anti-cancerous drug 5-FU by formulating multicore W/O/W nanoemulsions. Their formulation showed improved efficacy and absorption efficiency when compared to a simple nanoemulsion oral drug delivery system. This efficient drug delivery and ability to solubilize hydrophilic drugs was achieved by formulating multicore nanoemulsions. The formulated multiple nanoemulsions have the ability to produce a stable drug-delivery system with low surfactant concentrations, neutral pH, and a variety of oils, allowing for long-term shelf stability and drug solubilization.

Both hydrophobic and hydrophilic drugs can be delivered and encapsulated by formulating multiple nanoemulsions, which is not possible with many traditional drug delivery methods [15, 16]. Furthermore, longer pharmacokinetic profile and

lower required dosages of both hydrophobic and hydrophilic drugs have been shown due to the durability of the multiple nanoemulsions as compared to conventional drug delivery systems [14, 17].

1.4 Components of nanoemulsion

Drug, oil and aqueous phases, surfactants and co-surfactants are used to prepare nanoemulsion. The physical and chemical properties of these components are taken into account in the formulation, their efficiency and *in-vitro* and *in-vivo* stability.

1.4.1 Oil phase

The choice of other ingredients in nanoemulsions is highly dependent on oil phase. It is critical to choose the right oil for nanoemulsion formulation in order to achieve the desired properties. The oil to be selected for preparation of desired nanoemulsion is highly reliant on the solubility of particular drug. A combination of fixed oil and medium chain triglyceride can be used in order to achieve strong drug loading and

List of oils used in nanoemulsion	
Sr. #	**Oils**
1	Captex 355 (Glyceryl Tricaorylate/Caprate)
2	Captex 200 (Propylene Dicaprylate Dicaprate Glycol)
3	Captex 8000 (Glyceryl Tricaprylate (Tricaprylin)
4	Olive oil
5	Ethyl oleate
6	Isopropyl myristate (Myristic acid isopropyl ester)
7	Soya been oil
8	Glyceryl triacetate
9	Sefsol 218 (Caprylic/Capric Triglyceride)
10	Isopropyl myristate (Tetradecanoic acid)
11	Sesame oil
12	Corn oil
13	Intermediate Chain Triglycerides (Labrafac)
14	Peceol (Glyceryl Oleate)
15	Methyl decanoate
16	Labrafac (medium chain triglyceride)
17	Maisine 35-1 (1-Monolinolein)
18	Capryol 90 (Propylene Glycol Monocaprylate)
19	Capmul MCM (Glycerol monocaprylate)
20	Witepsol
21	Myritol 318

Table 1.
List of oils used as oil phase in nanoemulsion formulation [19].

emulsification. Only those oils should be used that resist auto-oxidation [18]. Due to their high lipophilicity and good solvent ability, medium chain triglycerides (MCT) (resistant to auto-oxidation) preferable over long chain triglyceride. Now adays, semi synthetic medium chain triglyceride are mostly used instead of medium chain triglyceride (**Table 1**) [19].

1.4.2 Surfactants

The type of surfactant used is determined by the type of nanoemulsion being prepared. The selection of particular surfactant is highly dependent on hydrophile–lipophile balance (HLB). Surfactants having low HLB value (<10) are lipophilic in nature and are used to formulate w/o nanoemulsions, while surfactants having high HLB (>10) value are hydrophilic in nature and are used to formulate o/w nanoemulsions (**Figure 2**).

To obtain nanoemulsions, sometimes a mixture of low HLB and high HLB surfactants can be needed. Surfactants are classified into 4 types to formulate a stable naoemulsion [19].

- Ionic surfactants,
- Cationic surfactants,
- Non-ionic surfactants,
- Zwitterionic surfactants (**Table 2**).

1.4.3 Co-surfactants

When surfactant fails to produce a stable formulation, Cosurfactant is usually used to lower the oil–water interfacial tension. Liquid crystalline phases form as the surfactant film becomes too stiff. By entering into the surfactant monolayer and destroying the liquid crystalline phases, co-surfactants increase the fluidity of the interfacial film [19]. Actually, low concentration of co-surfactant is required to formulate nanoemulsion. Short and medium chain alcohol (C3–C8) are often used as co-surfactant. They actually reduce the interfacial tension and increase the fluidity of interface of the nanoemulsion system (**Table 3**) [8].

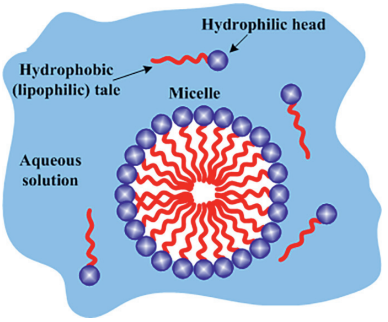

Figure 2.
Surfactant molecular structure [20].

List of surfactants used in nanoemulsions	
Sr. #	**Name of surfactants**
1	Tween 80 (Polyoxyethylene (20) sorbitan monooleate)
2	Tween 20 (Polyoxyethylene (20) sorbitan monolaurate)
3	Span 80 (Sorbitan monooleate)
4	Span 20 (Sorbitan monolaurate)
5	Span 60 (Sorbitan monostearate)
6	Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil)
7	Poloxamer 407 (Poly (ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol).
8	Poloxamer 188 ((Poly (ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol).
9	PEG 400 (Polyethylene glycol 400)
10	PEG 4000 (Polyethylene glycol 4000)
11	PEG 6000 (Polyethylene glycol 6000)
12	Capryol 90
13	Emulphor-620

Table 2.
List of surfactants used to formulate nanoemulsions [19].

1.4.4 Aquous phase

The nature of aquous phase also affect the droplet size and stability of nanoemulsion, like pH, electrolytes and ionic content of aquous phase. Distal water, ringer's solution, simulated gastric and intestinal fluids and phosphate buffer saline will also be used as aquous phase for nanoemulsion preparation. Similarly pH of aquous phase also effect stabilty and phase behavior of nanoemulsion, specially when a drug having pH dependent solubility is used in the formulation [8].

1.4.5 Co-solvents

Sometimes co-solvents are also used to formulate nanoemulsion so that to improve solubilty of either drug or hydrophilic surfactent in the oil phase. They make the formulation more lipophilic by lowering the water's dielectric constant. Organic solvents are mostly used as co-solvents such as glycerol, gasoline, propylene glycol (PG), and polyethylene glycol (PEG) [8].

1.5 Methods of nanoemulsion preparation

High and low energy methods are usually used to prepare nanoemulsion or combination of both. In case of high energy methods, a large distracting force is applied by means of mechanical devices like ultrasonicators, microfuidizers, and high-pressure homogenizers. This result in the production of vary small size droplets. However, Low-energy approaches do not use an external force to produce nanoemulsions; instead, they depend on the system's intrinsic physiological properties. The high energy methods are discussed one by one [8, 21].

List of co-surfactants used in nanoemulsion	
Sr. #	**Name of co-surfactants**
1	Propyl alcohol ($CH_3CH_2CH_2OH$)
2	Ethyl alcohol (CH_3CH_2OH)
3	Transcutol P (Diethylene glycol monoethyl ether)
4	Propylene glycol (Propane-1,2-diol)
5	Glycerin or Glycerol ($CH_2OHCHOHCH_2OH$)
6	Polyglyceryl oleate (poly (oxyethylene) 1,2,3-propanetriyl ester)
7	Propylene glycol laurate (propylene glycol dodecanoate)
8	Apricot kernel oil PEG-6 esters (O-CH_2-CH_2) n where n = 6
9	Propylene glycol monolaurate ($CH_3(CH_2)10COOCH_2CH(OH)CH_2OH$)
10	Medium chain mono- and diglycerides of caprylic acid (2,3-dihydroxypropyl octanoate (for monoglyceride); 1,2,3-propanetriol, di(caprylate) (for diglyceride)
11	Diethylene Glycol Monoethyl ether (2-(2-ethoxyethoxy) ethanol))

Table 3.
List of co-surfactants used in nanoemulsion [19].

1.5.1 High-pressure homogenization

This technique can be used to create nanoemulsions with droplet sizes as small as 1 nm (**Figure 3**). In high-pressure homogenization process, many forces are involved in the creation of nanoemulsion which was achieved by using high pressure homogenizer or piston homogenizer. Cavitation, a lot of turbulence, and hydraulics are a few of them. For the development of nanoemulsion droplets of small size, this process necessitates the use of high energy. Different techniques may be used to improve emulsification. Instead of using a single surfactant, mixture of several surfactants is more applicable so that to reduce surface tension. In order to achieve further small size droplets of the formulation, surfactants may be dissolved in the disperse phase rather than dispersion medium [23]. This method is applicable at both large- and small-scale production of naoemulsion. The method is appealing and effective, but high energy loss as the temperature rises during the manufacturing process (**Figure 4**) [24, 25].

1.5.2 Ultrasonic emulsification

Actually, ultrasonic emulsification is very effective at decreasing the size of droplets. The energy for ultrasonic emulsification is provided using sonotrodes called sonicator probes. It has a piezoelectric quartz crystal that expands and contracts in response to changing electric voltage. A mechanical vibration is produced as the sonicator tip comes in contact with the formulation, resulting in cavitation. The formation and collapse of vapors cavities in formulation is known as cavitation. Therefore, ultrasound can be used directly to formulate nanoemulsion. This method is mostly applicable on small scale production of nanoemulsion, where emulsion droplet sizes as small as 0.2 μm can be achieved [8]. This method is preferred because less concentration of surfactant and less energy is required to formulate nanoemulsion of homogenous nature, compared to other methods [26].

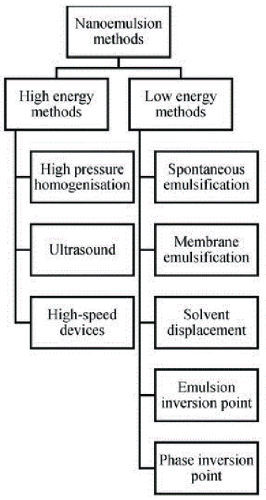

Figure 3.
Methods of nanoemulsion preparation [22].

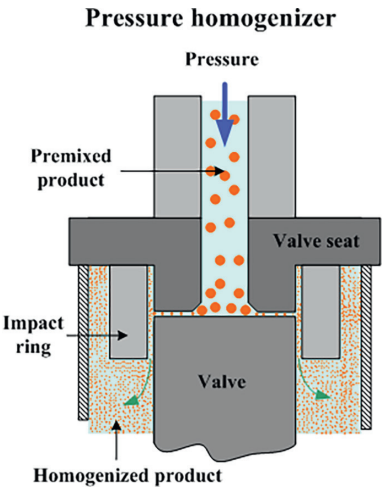

Figure 4.
Pressure homogenizer [24].

1.5.3 High-shear stirring

Nanoemulsions were first made with high-shear mixers and rotor-stator devices (**Figure 5**). High shear stirring is also known as high shear mixer, high shear homogenizer, rotar-stator mixer and high shear reactor. The internal phase droplet size can be reduced dramatically by raising the mixing strength in these machines, but it is difficult to prepare emulsions with average droplet sizes <200–300 nm. Colloid mills are used to achieve increase shear stress during dispersion. The most famous are Silverson flow mixers, which have different configurations for rotors and stators to accomplish more effective emulsification [28].

Ist of all as a result of high rotar speed, a high rotational speed is generated inside crumbling unit and the emulsion molecules are sucked into the rotor-stator assembly.

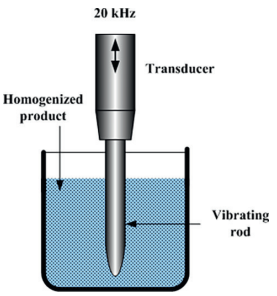

Figure 5.
Ultrasonic homogenizer [27].

Figure 6.
high-shear mixer [30].

After this the emulsion is thrown away to the periphery by centrifugal force, causing extreme turbulance, agitation, and dispersion in the gap between inner rotor and outer stator. Meanwhile, the emulsion flow at high speed over the stator's outer opening and leave the assembly. When the efficiency of high- shear stirring decrease dramatically while using viscous media in emulsion, the portion of internal phase increased and size of globules may exceed to 1 micrometer [29].

1.5.4 Microfluidization

In this process a device known as microfluidizer which employs a high-pressure positive displacement pump (500–20,000 psi), is used to produce nanoemulsion of vary small size (**Figure 6**). This positive displacement pump, pump the fluid into a specially designed chamber (consist of microchannels) at very high speed. After that, the product pushes through microchannels into a collission area, where very small particles in the nm range are formed. In this method, a microemulsion that has already been prepared is inserted into the microfluidizer, resulting in a nanoemulsion with the desired properties is obtained (**Figure 7**) [31].

1.5.5 Membrane emulsification

Membrane emulsification has gotten a lot of attention in the last 10 years, and it has a lot of possible applications. In this process, the internal phase is squeeze out through microchannels or small pores in a membrane having a uniform pore-size distribution into the dispersion medium using a low pressure. The size of the resulting globules is mainly determined by the membrane used, rather than agitation. This

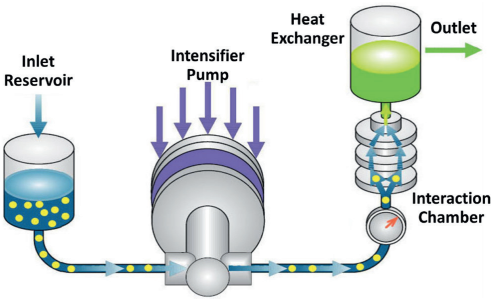

Figure 7.
microfluidization method [31].

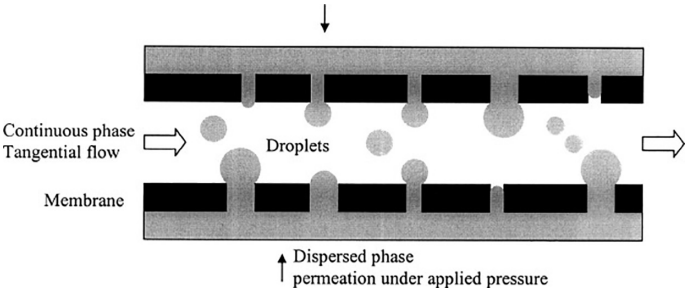

Figure 8.
Schematic diagram of membrane emulsification process [33].

method is highly applicable because of its easiness, use of less surfactant conc and lower energy requirement, and very small/uniform particle-size distributions. This technique is used to formulate both o/w and w/o emulsions [32].

2. Conclusion

Nanoemulsions represent a versatile and promising platform for drug delivery, offering numerous advantages over traditional dosage forms (**Figure 8**). The ability to encapsulate both hydrophilic and lipophilic drugs, along with their enhanced bioavailability and controlled release properties, makes nanoemulsions an attractive option for pharmaceutical formulations. Furthermore, the development of multiple nanoemulsions opens up new possibilities for complex drug delivery systems with specified phases and internal compartments, allowing for the encapsulation of multiple cargos simultaneously. Despite the challenges associated with nanoemulsion formulation and preparation, ongoing research efforts continue to explore novel methods and applications to further enhance their effectiveness and utility in various fields. Overall, nanoemulsions hold great promise for advancing drug delivery technologies and improving patient outcomes.

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Author details

Muhammad Rehan Malik[1,2*], Asif Nawaz[1] and Wajiha Noor[3]

1 Faculty of Pharmacy, Gomal Center of Pharmaceutical Sciences, Gomal University, Dera Ismail Khan, KP, Pakistan

2 Department of Pharmacy, The University of Chenab, Gujarat, Pakistan

3 University of Lahore, Gujrat Campus, Pakistan

*Address all correspondence to: malicrehan@gmail.com

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