Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(12):966-976

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Nanoemulsion: An excellent mode for delivery of poorly soluble drug through different routes

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ABSTRACT

Approximately 40% of new chemical entities are hydrophobic in nature and delivery of poorly water-soluble drugs takes the subject of much research. Formulation scientists confront a major challenge to formulate of highly lipophilic drugs because of the poor oral bioavailability. Nanoemulsion drug delivery system is one of the promising technologies, which is being applied to enhance the solubility and bioavailability of lipophilic drugs as well as deliver drugs at controlled rate and at target site. Nanoemulsions are submicron sized emulsion and consist of two immisible phase; one phase is oil phase other is aqueous phase. Size and shape of the particles dispersed in the continuous phase make distinction between the nanoemulsion and emulsions. The stability of nanoemulsion formulations can be maintained by a surfactant and co-surfactant. Clarity, high stability, and ease of preparation are the major advantages of Nanoemulsions. The present review emphasizes on overall advantage and disadvantage, various methods of preparation, characterization techniques and the various applications of sub micron size nanoemulison in different areas such as various route of administration, in chemotherapy, in cosmetic, etc.

Keywords: Nanoemulsions, Drug delivery, lipophilic drugs, Surfactant, Droplet Size.

INTRODUCTION

A nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of two immiscible liquid phases such as an oil phase and a water phase [1]. An interfacial tension, exists between the two liquids everywhere they are in contact due to differences in attractive interactions between the molecules of the two liquid phases [2]. Amphiphilic surface-active molecules, or surfactants are added to reduce this interfacial tension [3]. Droplet size of nanoemulsion falls typically in the range of 20-200 nm and shows a narrow size distribution [4]. The key difference between emulsions and Nanoemulsions are that the former exhibit excellent kinetic stability, are fundamentally thermodynamically unstable as well as emulsions are cloudy while Nanoemulsions are clear or translucent [5].

Types: Both composition and morphological characters are considered for classifying emulsion. Depending on the composition, three types of Nanoemulsions are most likely to be formed:

- Oil in water(O/W) Nanoemulsions wherein oil droplets are dispersed in the continuos aqueous phase;
- Water in oil Nanoemulsions(W/O) wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous Nanoemulsions wherein microdomains of oil and water are interdispersed within the system.

Surfactants or combination of surfactants and/or co-surfactants are used to stabilize the interface of all three types of Nanoemulsions. In all three types of Nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants [6].

Advantages:

- No creaming or sedimentation occurs on storage due to very small droplet size. The very small droplet size reduces the gravity force and induction of Brownian motion may be sufficient for overcoming gravity.
- The small droplet size prevents any flocculation of the droplets and their coalescence. That's why the system to remain dispersed with no separation.
- The large surface area of the nanoemulsion system allows rapid penetration of actives ingredients through the skin.
- Nanoemulsions give pleasant aesthetic character and skin feel for their transparent nature of the system, their fluidity (at reasonable oil concentrations) as well as the absence of any thickeners.
- Nanoemulsions are usually formulated by using reasonable concentration of surfactants, which are approved for human consumption (GRAS). A surfactant concentration in the region of 5% - 10% may be sufficient for preparing a 20% o/w nanoemulsion.
- Low surface tension of the whole system enhances the wetting, spreading and penetration of droplets.
- Nanoemulsions can be applied for delivery of fragrant and could also be applied in perfumes, which are desirable to be formulated alcohol free [7,8].
- Water solubility and ultimate bioavailability of lipophilic drugs can be improved by using nanoemulsion.
- The nano-sized droplets would influence the transport properties of the drug. This an an important factor in sustained and targeted drug delivery [9].
- Reproducible data in plasma concentration profiles and bioavailability of drugs can be made by nanoemulsions [10].
- Minimizing irritation frequently encountered with extended contact of the drug and gut wall due to fine oil droplets. Because fine oil droplets promote wide distribution of the drug throughout the intestinal tract [11].
- Nanoemulsions offer rapid onset of action and reduced intersubject variability in terms of GIT fluid volume over existing self-emulsifying system [12].
- Most nanoemulsions appear optically transparent, even at large loading due their structures which are much smaller than the visible wavelength [13].
- Peptides drugs are undergo enzymatic hydrolysis in GIT. But nanoemulsions have potential to deliver peptides [14].
- Drugs can be delivered through multiple routes like topical, oral and intravenous.
- Masking the unpleasant taste of active drugs is possible.
- Increases patient compliance.
- Both lipophilic and hydrophilic drugs can be carried by same nanoemulsion [15].

Disadvantages:

- High pressure homogenisers, ultrasonics, microfluidiser and other special application techniques are required for nanoemulsions preparation. Such equipment (such as the Microfluidiser) became available only in recent years.
- High cost of commercial production especially for cosmetic industry because of using expensive equipment as well as high concentrations of emulsifiers.
- It is difficult to understand the role of surfactants and cosurfactants and also the mechanism of production of submicron droplets.
- Classical macroemulsion systems provides better benefits than using nanoemulsions
- The interfacial chemistry is important factors for the production of nanoemulsions. But the function of the interfacial chemistry is not clear [7, 8].
- Difficult for high-melting substances due to their limited solubility.
- Stability of nanoemulsions are affected by environmental parameters such as temperature and pH [15].

Components of nanoemulsion:

Nanoemulsions are consisted of following main three components:

1. Oil
2. Surfactant

3. Co-surfactant
4. Aqueous phase

Oil phase:
Oil phase influences the selection of other ingredients of nanoemulsions. To get desired characteristics of nanoemulsion, it is important to select the appropriate oil phase.

- The choice of oily phase is depends on its ability to solubilize the selected drug candidate and its ability to facilitate formation of nanoemulsion of desired characteristics.
- Good balance between drug loading and emulsification can be obtained by using a mixture of fixed oil and medium chain triglycerides.
- Oil phase should be selected that resist the oxidative degradation [16].
- On weight basis medium chain triglycerides (MCT) have higher solvent capacity and resistance to oxidation compare to long chain triglycerides due to their high lipophilicity and their solvent capacity for drugs [17].
- Recently, semi-synthetic medium chain triglycerides become good replace of medium chain triglycerides.
- Modified vegetable oils, digestible or non-digestible oils and fats such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, hydrogenated soybean oil, peanut oil and beeswax are also used as oil phase [18].

Table 1. List of oils used in nanoemulsions

Sl.No	Oils
01	Captex 355 (Glyceryl Tricaorylate/Caprate)
02	Captex 200 (Propylene Dicaprylate/Dicaprate Glycol)
03	Captex 8000 (Glyceryl Tricaprylate (Tricaprylin)
04	Witepsol (90:10 % w/w c12 Glyceride tri: diesters)
05	Myritol 318 (c8/c10 triglycerides)
06	Isopropyl myristate (Myristic acid isopropyl ester)
07	Capmul MCM (Glycerol monocaprylate)
08	Carbitol (Glycerol triacetace)
09	Sefsol 218(Caprylic/Capric Triglyceride)
10	Peceol (Glyceryl Oleate)
11	Maisine 35-1 (1-Monolinolein)
12	Labrafac (Medium Chain Triglycerides)
13	Capryol 90 (Propylene Glycol Monocaprylate)
14	Isopropyl myristate (Tetradecanoic acid)
15	Sesame oil
16	Soya bean oil
17	Olive oil
18	Corn oil
19	Castor oil
20	Methyl decanoate
21	Ethyl oleate

Surfactants:
The choice of surfactant is depends on the type of nanoemulsion is prepared. Surfactants with an HLB value <10 are hydrophobic in nature and used to prepare w/o nanoemulsion whereas high HLB (>10) surfactants are hydrophilic in nature and used to prepare o/w nanoemulsion. In some case, mixture of low HLB and high HLB surfactants may be required to get nanoemulsions [19]. The following surfactants used to stabilise systems:

- Non-ionic
- Zwitterionic
- Cationic
- Anionic surfactants

Nanoemulsion region can be effectively extended by the combinations of ionic and non-ionic surfactants. Examples of non-ionics include polyoxyethylene surfactants such as Brij 35 (C12E35) or a sugar esters such as sorbitan monooleate (Span 80). Zwitterionic surfactants exhibit excellent biocompatibility such as phospholipids [20,21,22,23]. The best known classes of cationic surfactants are Quaternary ammonium alkyl salts form with hexadecyltrimethyl ammonium bromide (CTAB) and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known. Sodium bis-2-ethylhexylsulphosuccinate (AOT) is twin-tailed anionic surfactant and effective stabiliser of w/o microemulsions [24].

Table 2: List of Surfactants used in nanoemulsions	
Sl.No	**Surfactants**
01	Capryol 90
02	Gelucire 44/14, 50/13
03	Cremophor RH 40
04	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
05	Labrafil M 1944 CS, M 2125 CS
06	Lauroglycol 90
07	PEG MW > 4000
08	Plurol Oleique CC 497
09	Poloxamer 124 and 188
10	Softigen 701, 767
11	Tagat TO
12	Tween 80
13	Labrasol
14	Poloxamer 407
15	Polaxmer 188
16	Emulphor-620

Co surfactants:
Most of the time, Cosurfactant is added to lower the oil-water interfacial tension sufficiently to yield a nanoemulsion when surfactant fails to do it effectively. When surfactant film is too rigid, it forms liquid crystalline phases. Cosurfactants provide additional fluidity to interfacial film by penetrating into the surfactant monolayer and disrupting the liquid crystalline phases [25]. Self-associated structures are not formed by cosurfactants like micelles on its own. Hydrophilic cosurfactants preferably alcohols of intermediate chain length are known to reduce the oil/water interface and allow the spontaneous formation of nanoemulsion. Examples of alcohols of intermediate chain length are hexanol, pentanol and octanol [26]. Medium chain length alcohols allow greater penetration of the oil into this region as well as increase the mobility of the hydrocarbon tail [27,28].

Table 3: list of Co Surfactants used in nanoemulsions	
Sl.No	**Co Surfactants**
01	TranscutolP
02	Glycerin,Ethylene glycol
03	Propylene glycol
04	Ethanol
05	Propanol
06	Polyglyceryl Oleate
07	Propylene Glycol Monolaurate
08	Diethylene Glycol Monoethyl ether
09	Medium chain mono- and diglycerides of caprylic acid
10	Propylene Glycol Laurate
11	Apricot kernel oil PEG-6 esters

Aqueous Phase:
The droplet size and stability of nanoemulsion is influenced by the nature of aqueous phase such as pH, ionic content of aqueous phase and electrolytes. Spontaneous nanoemulsification of nanoemulsion is evaluated by using plain water, Ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8) and phosphate buffered saline can be used as aqueous phase. Among the above properties of aqueous phase pH of the aqueous phase can have a dramatic influence on the phase behavior of nanoemulsions when a drug with pH-dependent solubility is loaded in the system.

Co-solvents:
Co-solvents are used to improve the dissolution of large quantity of either the hydrophilic surfactant or the drug in the lipid base by co-solvency. They also induce more hydrophobic environment by reducing the dielectric constant of water. Organic solvents are suitable for oral delivery such as as ethanol, glycerol, propylene glycol (PG), polyethylene glycol(PEG) [29]. Alcohols and other volatile co-solvents have evaporating problem. Thus, alcohol free formulations have been designed [30].

Solubility study:
The solubility of the drug in various oils, surfactants, cosurfactants and combination of oils is important for preparing a successful nanoemulsion. The solubility is determined by dissolving an excess amount of the drug in

small quantities of the selected oils, surfactants, cosurfactants, combination of oils and mixed using a mixer. An isothermal shaker is used to equilibrate the mixtures at ambient temperature and then samples are removed from the shaker and centrifuged. A 0.45 μm membrane filter is used to filter the supernatant. The concentration of the drug is determined in each oil, surfactant, cosurfactant and combination of oils by using suitable assay method at their respective λmax [31].

Phase inversion method

Phase inversion temperature (PIT) method was introduced by Shinoda et al. This method was based on the changes of solubility of polyoxyethylene- type surfactant with temperature. With increase temperature this surfactant becomes lipophilic. Lipophilicity of polyoxyethylene- type surfactant in increased is due to dehydration of polymer chain. polyoxyethylene- type surfactant monolayer has a large positive spontaneous curvature forming oil-swollen micellar solution phase at low temperature. In this method chemical energy is used for getting fine dispersion. This chemical energy is resulting of phase transitions taking place through emulsification path. The adequate phase transitions depend on temperature and the composition. Varying the composition at constant temperature or by varying the temperature at constant composition can be followed to produce adequate phase transitions [32].

Sonication method:

Sonication method is another best way to prepare nanoemulsion where sonication mechanism is used to reduce the droplet size. This method allows for both large batches and small batches of nanoemulsion [33].

Ultrasonic System

In ultrasonic emulsification, sonotrodes (sonicator probe) is used to input energy. Sonotrodes contains piezoelectric quartz crystals which can be expand & contract in response to alternating electrical voltage. As the tip of sonicator probe contacts the liquid, cavitations (Cavitation is the formation and collapse of vapour cavities in a flowing liquid) occurs due to the generation of mechanical vibration. When the local pressure is reduced at that temperature of the flowing liquid, a vapour cavity is formed due to the changes of local velocity. Powerful shock waves are radiated throughout the solution in proximity to the radiating face of the tip when these cavities are collapsed. This causing the breaking of dispersed droplets. This power available varies inversely with the frequency within the ultrasound range(0-200kHz). To produce emulsion, Ultrasound can be directly used. A large amount of energy is required to break down an interface. Before applying acoustic power, it is better to prepare coarse emulsion. The ultrasound emulsification process is mainly applied in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained [34].

Microfluidizer

In this method emulsion is produced under high pressures up to approximately 700 Mpa. The nozzle of microfludizer acts as the interaction chamber. Two jets of crude emulsion from two opposite channels collide with one another. a pneumatically powered pump is used to deliver the process stream. This process stream is capable of pressurizing the in-house compressed air (150-650 Mpa) up to about 150 Mpa. A tremendous shearing action is formed by forcing the flow stream through microchannels toward an impingement area, which can provide an exceptionally fine emulsion [35].

Jet Disperser

Mechanism of Jet Disperser is similar to microfludizer but at a different design. The diameter of the bores in jet dispersers are typically 0.3-0.5mm. An “orifice plate” is used as a homogenizing nozzle. The inlet head diameter of orifice plate is typically 10-60nm. Jet dispersers and orifice plate contain no moving parts. So they can be used at high pressures up to 300-400 Mpa. This is the main difference between Jet Disperser and microfludizer. In jet dispersers and orifice plates, laminar elongation flow ahead of the bores disrupted the droplets into smaller size [36].

CHARACTERIZATION

Characteristics of nanoemulsions will depend on preparation method. Following parameters should be analyzed at the time of preparation of nanoemulsion.

Phase behavior study:

Phase behavior study is crucial for these nanoemulsions that are prepared by phase inversion Temperature and self emulsification method and used to determine the phase of nanoemulsion, dispersibility and for the optimization of ingredients (surfactant, oil phase and aqueous phase). This study is done by placing the different ingredients of

nanoemulsion in glass ampoules at varying the concentration. Then all ingredients are thoroughly homogenized at a certain temperature for a time until equilibrium. An isotropic phase can be identified by polarized light is used to identify an isotropic phase [37].

Particle Size Analysis:
Dynamic light scattering (DLS) method are used for the measurement of particles and particle size distribution. The average droplet size of the nanoemulsions were determined by dynamic light scattering using zetasizer which measures the Brownian motion of the droplet and its relation to the droplet size based on the principle that larger droplets have a slower motion [38].

Polydispersity index and zeta potential analysis
The stability of nanoemulsion is also indicated by the zeta potential. Because zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particles in a dispersion. A high zeta potential will confer stability. Malvern Nano-Zetasizer is used to determine the zeta potential of the selected nanoemulsion formulations [39].

Table 4: Reference values of Zeta potential

Zeta potential [mV]	Stability behavior of the colloid
from 0 to ±5,	Rapid coagulation or flocculation
from ±10 to ±30	Incipient instability
from ±30 to ±40	Moderate stability
from ±40 to ±60	Good stability
more than ±61	Excellent stability

Uniformity of droplet size within the formulation is detected by Polydispersity index. Polydispersity is the ratio of standard deviation to mean droplet size and higher the polydispersity, the lower the uniformity of the droplet size in the formulation [40].

Analysis of components interactions:
Interactions of different components can be understood by using Differential Scanning Calorimetry (DSC) [41].

Viscosity, Conductivity and Dielectric measurements:
Viscosity should be measured to ensure the better delivery of the formulation as well as determine the shape of micelles. Conductivity measurements provide information about continuous phase such as oil-continuous or water-continuous, as well as providing phase inversion phenomena. The higher conductivity of nanoemulsion indicates larger percentage of water which allows more freedom for mobility of ions. If the conductivity of formulations remain constant even after storage of one month at room temperature, which indicates the stability of formulations with no sign of phase inversion. Structural and dynamic features of nanoemulsion system can be proved by dielectric measurements. The higher conductivity of nanoemulsion indicates larger percentage of water which allows more freedom for mobility of ions. If the conductivity of formulations remain constant even after storage of one month at room temperature, which indicates the stability of formulations with no sign of phase inversion [42].

Polarity Analysis:
Emulsification efficiency is depends on the polarity of nanoemulsion droplets. Some factors such as HLB value of surfactants, molecular weight of the hydrophilic portion, chain length and degree of unsaturation of fatty acids, concentration of the emulsifier may affect the polarity of the oil droplets. Affinity of the drug compound for oil and/ or water, the type of forces formed as well as release of the drug into the aqueous phase is depends on the polarity of droplets [43].

Drug contains:
Western Blot method is widely to determine the amount of drug contained in the formulation. The amount of drug is calculated from calibration curve [44].

pH:
The pH of the drug loaded nanoemulsion is determined by using a digital pH meter. pH should to meet the specific requirement. For example, pH of the skin is in the range of 5.5 to 7.0, so pH of the formulation for topical application should be optimize within the range [45].

Droplet size and size distribution:
Droplet size is determined by photon correlation spectroscopy (PCS). The fluctuations in light scattering due to Brownian motion of the droplets are analyzed by PCS using a Zetasizer. Droplets size is determined based on the principle that larger droplets have a slower motion. In this method the formulation is dispersed in water (required amount) in a volumetric flask and then mixed thoroughly with vigorous shaking. Light scattering is monitored at 25 °C a 90 ° angle [46].

Stability of Nanoemulsion during Storage
The effect of temperature and humidity on the optimum formulation of nanoemulsion is evaluated for 3 months after storing at 5°C±3°C and 25°C±2°C/60%±5% RH and 40°C±2°C /75%±5%. The drug content in the nanoemulsions is determined by spectrophotometrically [47].

Refractive index: Abbe´s refractometer is used to determine the refractive index at 25±0.5°C [48].

STABILITY STUDY
Thermodynamic stability studies:
Heating cooling cycle: Six cycle between refrigerator temperature 4°C & 45°C with storage at each temperature. The study is continued more than 48 h. Centrifugation test is performed if the formulations are stable at these temperatures.

Centrifugation: Stable formulations are centrifuged at 3500 rpm for 30 min. if there is no phase separation occur in the formulations, Those formulations will be taken for freeze thaw stress test.

Freeze thaw cycle: Three freeze thaw cycle between -21°C & 25°C with storage at each temperature for not less than 48 h is done for the formulation. Dispersibility test for assessing the efficiency of emulsification is done for those formulations which will passé thermodynamic stress test [49].

PH stability: The nanoemulsion dispersion are kept in air tight containers and stored at different pH condition for 2 hours and the then sample is withdrawn. The supernatant are analyzed by reported assay method after centrifugation [50].

ENTRAPMENT EFFICIENCY
Method 1: Unentrapped drug is separated by dialysis, centrifugation, or gel filtration from nanoemulsion dispersion. Vesicle is disrupted by using 50% n-propanol or 0.1% Triton X-100 and the resultant solution is analyzed by appropriate assay method for the drug. Following equation is used to determine the % Entrapment efficiency.

% Entrapment efficiency (% EF) = (Amount of drug entrapped/ total amount of drug) x 100 [51].

Method 2: Separation of unentrapped drug is done by dialysis, centrifugation, or gel filtration method. The supernatant was diluted with 5 ml of phosphate buffer pH 7.4. From the above solution, 1 ml is taken and transferred to 10 ml standard flask and made up to 10 ml with phosphate buffer pH 7.4. The resultant solution is analyzed by appropriate assay method using phosphate buffer pH 7.4 as blank. The percentage of drug encapsulation was calculated by the following equation:

EE (%) = [(Ct - Cf)/Ct] 100

Where Ct is the concentration of total drug and Cf is the concentration of unentrapped drug [52].

IN VITRO RELEASE
Method 1: Glass tube of diameter 2.5cm with an effective length of 8cm which is previously covered with cellophane membrane is used to determine the in vitro release rate. Measured amount of nanoemulsions are placed in the cylinder which is placed in 100 ml of phosphate buffer saline, pH 7.4. This phosphate buffer saline acts as receptor compartment. The temperature of receptor medium was maintained at 37±1°C and agitated at 100rpm speed using magnetic stirrer. Aliquots of 5ml sample are withdrawn from receptor compartment at intervals of 24 h for 3 days. An equal volume of phosphate buffer saline, pH 7.4 is added to receptor compartment to maintain its

volume in each sampling time. The drug in withdrawn samples is estimated by the reported assay method using medium as blank [53].

Method 2: Method of in-vitro release is studied by the use of dialysis bag (pore size of dialysis bag depends on MW of drug)After separating the unentrapped drug, the nanoemulsion suspension containing drug equivalent to drug content is pipette into dialysis bag which is previously socked and washed several times with distilled water. This is placed in 100 ml of phosphate buffer saline pH 7.4 and kept with constant agitation on a magnetic stirrer maintaining a temperature of 37^0 C. In each periodical time the reported amount of sample is withdrawn and same volume of fresh sample is replaced. Then samples is assayed reported assay method using medium as blank. The release was compared with pure drug solution [54].

APPLICATIONS

Nanoemulsions are of great interest not only in Pharmaceutical but also in Nutraceuticals, Food products & cosmetics formulation. Nanoemulsions are used to deliver drugs through various routes such as Parentral, Oral, Topical, Ocular, Pulmonary, Mucosal, Cosmetic, Transdermal, Controlled &Target delivery.

Parenteral route:

Nanoemulsion are advantages for intravenous administration due to its nano-size droplets. In addition, both O/W and W/O Nanoemulsion can be used for parenteral delivery. Lipid nanoemulsion has been widely explored for parentral delivery of drugs.

Nasal Route:

Nanoemulsions increase absorption and prolong the contact time between emulsion droplets and nasal mucosa. Nasal absorption of drug from nanoemulsion is compared with aqueous suspension. Example of drugs which have been formulated for nasal delivery are insulin, testosterone and rennin-inhibitor.

Ocular Delivery:

Desired bioavailability and patient comfort can be obtained by loading lipophilic drug in o/w ocular nanoemulsions. Following drugs are given topically into the eye e.g. Piroxicam, pilocarpine, indomethacin, cyclosporine A [55].

Nanoemulsion in Cell Culture Technology:

Nanoemulsions help to increase uptake of oil soluble component in cell culture and improve growth of culture cell. That's why nanoemulsions are used in cell culture technology.

Prophylactic in Bio-Terrorism Attack:

Prophylactic medications are formulated in nanoemulsion. Nanoemulsion can be used against bio-attack pathogens such as anthrax, Ebola and contaminated wounds to salvage limbs [56, 57].

Nanoemulsions in Cancer Therapy:

In case of cancer chemotherapy, nanoemulsions are used as vehicle for rate controlling prolong drug release after intramuscular and intratumoral injection (W/O systems) [58, 59].

Nanoemulsion to enhance skin penetration:

Organic solvents are used to enhance the skin penetration of poor efficacious drugs. But these solvents induce some adverse effects on the skin such as skin irritation, toxicity and sensitization.

To avoid these adverse effects, drug is entrapped in the o/w nanoemulsion without using topical organic solvents. In addition, o/w nanoemulsion allows high soluble capacity for water insoluble topically active medicaments and also aids in carrying water, an excellent softener, to the skin e.g. NSAIDs, diazepam, α-tocopherol, antifungal drugs (econazole or miconazole nitrate) [60].

Pulmonary Delivery:

Formulation of microemulsions incorporating Salbutamol drug for pulmonary delivery by using pressurized aerosol system. Lecithin is used to stabilize formulation [61].

Antimicrobial Nanoemulsions:
Broad spectrum activity of nanoemulsion has been seen against bacteria (e.g., E. coli, Salmonella, S. aureus), enveloped viruses (e.g., HIV, Herpes simplex), fungi (e.g., Candida, Dermatophytes), and spores (e.g., anthrax). The nanoemulsion particles are thermodynamically driven to fuse with lipid-containing organisms and this fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen. After fusion they release part of the energy trapped within the emulsion. Cell lyses and death of micro-organisms occurs due to the destabilization of the pathogen lipid membrane [62, 63, 64].

Oral Drug Delivery System:
A nanoemulsion can incorporate hydrophobic drug in oil droplets and due its very small particle size, it be used to improve oral bioavailability of poorly to soluble drug. Drugs such as steroids, hormones, diuretic and antibiotics can be delivered in nanoemulsion form through oral route.

Nanoemulsion as Mucosal Vaccines:
Needle free immunization can be done by nanoemulsions containing recombinant protein and inactivated organism and deliver to a mucosal surface for facilitating uptake by antigen-presenting cells [65].

Transdermal Drug Delivery System:
Nanoemulsion carrying water(an excellent softener) to the skin and increase drug permeation through the skin. That's why nanoemulsion can be used for delivery of drug through transdermal route [66].

CONCLUSION

Nanoemulsions offer multiple advantages for the delivery of poorly soluble drugs. They also offer efficient targeting and controlled drug delivery as well as protection of the encapsulated bioactive materials. Simple technology is used to prepare nanoemulsion and its droplet size is reduced to the nano-scale levels, which leads to some very interesting physical properties. The importance of design and development of nanoemulsion is increasing day by day for commercial purposes. Future perspectives of nanoemulsions are very promising in different fields of therapeutics as well as cosmetics.

Acknowledgement
We are certainly grateful to Professor Dr. Kohinur Begum, Chairman, Department of Pharmacy, Asa University Bangladesh and Professor Dr. Reza-ul Jalil, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Bangladesh for providing the idea. We are also thankful to Professor Dr. Md. Ehsanul Huq, Department of Pharmacy, Primeasia University for his support to prepare this article.

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