

## Review

Kumar Bishwajit Sutradhar\* and Md. Lutful Amin

# Nanoemulsions: increasing possibilities in drug delivery

**Abstract:** Nanotechnology, the science of nano sized particles, has rapidly gained the spotlight in diversified areas including pharmaceutical sector. With the blessings of accurate drug designing and better pharmacological action, it has entered the pharmaceutical arena bringing promising discoveries along with it. Nanoemulsion is one of the greatest and advantageous dosage forms with the application of nanotechnology in pharmaceutical formulations. Very small size droplets of the nanoemulsion favor better drug absorption and targeting. It not only improves the conventional emulsion systems but also opens new opportunities for other drugs to be designed more precisely with better bioavailability and accurate dosing rendering minimum side effects. This article depicts various advantageous features of nanoemulsions delineating different methods of preparation. The foci of this review also include the opportunities of other drugs to be formulated through nanoemulsification in order to ensure better therapeutic effect. The summary shows recent researches on nanoemulsion formulation from different classes of drugs as well as some formulations based on nanoemulsion templates. The methods of preparing nanoparticles, characterized by nanoemulsion templates, have also been discussed which, as a whole, presents the best possibilities of nanoemulsions.

**Keywords:** emulsification method; nanocarrier; nanoemulsion template; nanoparticle; phase inversion.

**\*Corresponding author: Kumar Bishwajit Sutradhar**, Senior Lecturer, Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka-1217, Bangladesh, Phone: +88 01911 089 806, E-mail: kumarbishwajit.pharm@gmail.com

**Md. Lutful Amin and Kumar Bishwajit Sutradhar:** Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka-1217, Bangladesh

## Introduction

The world of biomedical science has recently changed significantly with the development of nanotechnology

which has enabled the scientists to think more precisely in designing better therapies. Nanotechnology is the science that deals with the particles of nano scale sizes. Use of nanotechnology in pharmaceutical sciences has emerged at a great extent from the last couple of years (1). Different sorts of pharmaceuticals currently being used or in the process of development by using nanoparticles include, nanoemulsions (NE) (submicron sized emulsions), nanosuspensions (submicron sized suspensions), nanospheres (drug nanoparticles in polymer matrix), nanocapsules (encapsulated drug nanoparticles), lipid nanoparticles (lipid monolayer enclosing a solid lipid core), dendrimers (nano sized three-dimensional branched molecules of polymer), nanotubes (sequence of nanoscale C60 atoms arranged in a long thin cylindrical structure), and nanoshells (concentric sphere consisting of a dielectric core and a metal shell) (2). Nanoemulsion is an emulsion system having the droplet size in nanometer scale in which oil or water droplets are finely dispersed in the opposite phase with the help of a suitable surfactant to stabilize the system (3, 4). The average droplet size usually ranges from 0.1 to 500 nm. The size of the droplets varies depending on the drug particles, mechanical energy, composition and relative amount of the surfactants (5). Nanoemulsions are also known as miniemulsions, fine-dispersed emulsions, submicron emulsions etc., which can be either O/W (oil in water) or W/O (water in oil) emulsion. The amount of oil in O/W nanoemulsions may vary but generally is within 5%–20% w/w. Sometimes a mixture of oils may be used to improve drug solubilization in the oil phase. A co-surfactant or a co-solvent may be used in addition to the surfactant to facilitate the stabilization process (6, 7). The significant property that differentiates the nanoemulsions from other emulsion systems is that, a nanoemulsion shows different pattern in physical and rheological properties with decreasing droplet size. Two major distinguishing advantages of a nanoemulsion are its stability and easy penetration. Due to very fine particle size and less surface tension between the oil and water molecules, it barely has the tendency to agglomerate or precipitate which reduces the possibility of creaming or sedimentation. As a result, a nanoemulsion is much more

stable than other emulsion systems and is more translucent compared to microemulsions (8). Historically, it has always been very difficult for most of the drug molecules to be absorbed easily from the gastrointestinal tract (GIT) or to cross the skin barrier. Development of nanoemulsion can solve this difficulty to a great extent since drug molecules in nanometer scale cross the barriers very well. This system can also be used as a precise drug carrier to deliver the drug in more specific and targeted areas.

Few nanoemulsions have been manufactured commercially in oral, topical, ophthalmic and even in intravenous (IV) drug delivery system. IV administration of nanoemulsions requires biodegradable surfactants. Numerous researches are presently being carried out in order to manufacture nanoemulsions from different classes of drugs for a variety of purposes. The use of nanoemulsion spreads from antibiotic therapy, atherosclerosis treatment, transdermal drug delivery and ophthalmic application to as far as cancer therapy, vaccine delivery etc. (2, 9). It can bring a great revolution in cancer treatment since it was always a difficult measure to destroy the cancer cells completely with minimal interference to the normal body cells (10). This compilation, illustrating the manufacturing methods as well as the recent researches, portrays the rising possibilities of nanoemulsions to serve the human being accurately with minimum damage.

## Classification

There are three types of nanoemulsions on the basis of composition of oil and water portions. a) Oil in water (O/W) nanoemulsions where oil droplets are dispersed in continuous aqueous phase b) Water in oil (W/O) nanoemulsions where water droplets are dispersed in continuous oil phase and c) Bi-continuous nanoemulsions where microdomains of oil and water are inter-dispersed within the system. In all three types of nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants (8). Based on the surfactants used, O/W nanoemulsions can be further classified into three types, which are neutral O/W nanoemulsion (neutral surfactants are used), cationic O/W nanoemulsion (cationic

surfactants are used) and anionic O/W nanoemulsion (anionic surfactants are used).

## Surfactants

Three kinds of surfactants are used in the preparation of nanoemulsions to stabilize the system (Table 1) (8). Every surfactant molecule has two parts, a hydrophilic head and a hydrophobic tail. The surfactants are classified on the basis of the polar groups present in their heads.

A nonionic surfactant has no charge group present in its head. The ionic surfactants carry net charges. If the charge is negative in its head, the surfactant is called anionic and if the charge is positive, it is called cationic. Typical examples of aqueous soluble surfactants are nonionic surfactants (e.g., Tween 20) which are preferred because they are usually less irritating than the ionic ones (11). Biodegradable emulsifiers are used in parenteral nanoemulsions. Some biodegradable surfactants are emulsifier egg, soy lecithin, and the oleaginous substrate (e.g., soybean, safflower, structured triglycerides or miglyol oil) (12).

## Oils and co-surfactants

Commonly used oils in nanoemulsion preparations are IPM (Isopropyl Myristate), glyceryl triacetate, propylene glycol mono ethyl ether etc. Medium chain triglycerides (MCT) are preferred over long chain fatty acids (11). Different co-surfactants are sometimes used to consolidate the stabilization process (Table 2 lists the examples of oils and co-surfactants used in nanoemulsions) (9).

## Advantages

There are numerous advantages of nanoemulsions over the conventional emulsion systems. Tiny droplet size of nanoemulsion prevents coalescence among the particles which ensures the least possibility of separating any phase as a distinct layer. There is no possibility of sedimentation or creaming by gravitational force because of very small size of the particles having minimum weight. Small

**Table 1** Types of surfactants with their examples.

Types	Examples
Nonionic surfactants	Fatty alcohols, glycerol esters, fatty acid esters etc.
Anionic surfactants	They contain carboxylate groups. Soaps, sulfonates, divalent ions etc.
Cationic surfactants	Amines and quaternary ammonium compounds such as cetyl trimethyl ammonium bromide.

**Table 2** List of oils and co-surfactants used in the preparation of nanoemulsions.

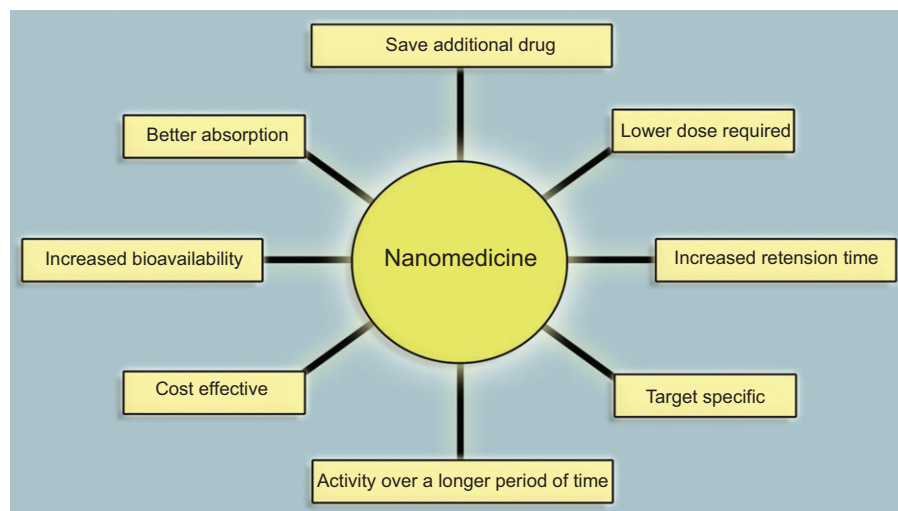
Chemical name	
Oils	Co-surfactants
Glyceryl triaorylate/caprata	2-(2-ethoxyethoxy)ethanol
Propylene glycol dicaprylate/dicaprate	Glycerin
Glyceryl tricaprylate (tricaprylin)	Ethylene glycol
90:10% w/w C12 Glyceride triesters	Propylene glycol
C8/C10 Triglycerides	Ethanol
Myristic acid isopropyl ester	Propanol

droplet size also ensures even dose distribution and a well dispersion system. Less amount of surfactant is required compared to other emulsion systems. It can increase the bioavailability of poorly soluble drugs since small particles easily cross the absorption membrane. Nanoemulsion can be formulated to administer drugs through various routes. Furthermore, very small size provides large surface area which eases the solubilization and penetration through the skin or epithelial layer (2, 7, 8). Faiyaz Shakeel and his research group developed O/W nanoemulsion of celecoxib, a highly lipophilic and poorly soluble drug with oral bioavailability of around 40% (capsule), for transdermal application. They found that the absorption of celecoxib through transdermally applied nanoemulsion and nanoemulsion gel was 3.30 and 2.97-fold higher as compared to oral capsule formulation (13). Nanoemulsion increases drug retention time in the target region hence, it causes less side effects or toxicities because it does not act on the unwanted areas of the body. Less amount of drug is required because of better penetration, increased bioavailability, increased retention time and less drug loss. It also facilitates parenteral application of emulsions having

tiny droplets (7, 8). Figure 1 below contains some basic advantages of nanoemulsion based nanomedicine. Sivakumar and co-workers observed that O/W nanoemulsion of aspirin, prepared by ultrasound cavitation techniques, produced better anti-inflammatory and analgesic activities than conventional formulations (14). A research team, led by Kesavan Bhaskar, developed nanoemulsion-based lipid nanoparticles for transdermal delivery of flurbiprofen. The bioavailability of flurbiprofen gel was found to increase 4.4 times compared to oral administration (15). The positively charged antimicrobial nanoemulsions have broad spectrum activity against various microorganisms. The nano droplets thermodynamically fuse with lipid containing microorganisms which is enhanced by electrostatic force between the cationic charge of nanoemulsion and anionic charge on the organisms. As a result, cell lysis occurs destabilizing the lipid membrane (2). Yu-Hsin Lin and his fellows demonstrated that positively charged W/O amoxicillin nanoemulsion, prepared with chitosan and heparin, produced better eradication of *Helicobacter pylori* than the conventional amoxicillin solutions (16).

### Formulation procedures

There are mainly four methods for the preparation of nanoemulsion. Each method differs significantly from others and the objective of each method is to gain the particle size within 500 nm with a stable emulsion system. Selection of any method depends on the type of drug and the dosage form. For producing nanoemulsions, surfactants must be chosen accurately so that an ultra low interfacial tension ( $<10^{-3}$  mN/m) can be obtained (8).



**Figure 1** Key advantages of nanoemulsion based nanomedicines.

## Microfluidization

It is a patented manufacturing technology where a device called microfluidizer is used (Figure 2). There is a high pressure displacement pump (500–20,000 psi) in this device which gets the materials pass through a chamber containing many microchannels. The materials move to an impingement area flowing through the microchannels and convert into very fine particles.

The liquid phases (oil phase and aqueous phase) are processed in an inline homogenizer to give a coarse emulsion. Then the coarse emulsion is passed through the microfluidizer to obtain the fine nanoemulsion. This process is continued repeatedly until the desired particle size is obtained. The nanoemulsion is then filtered under nitrogen to remove the larger particles (2, 7).

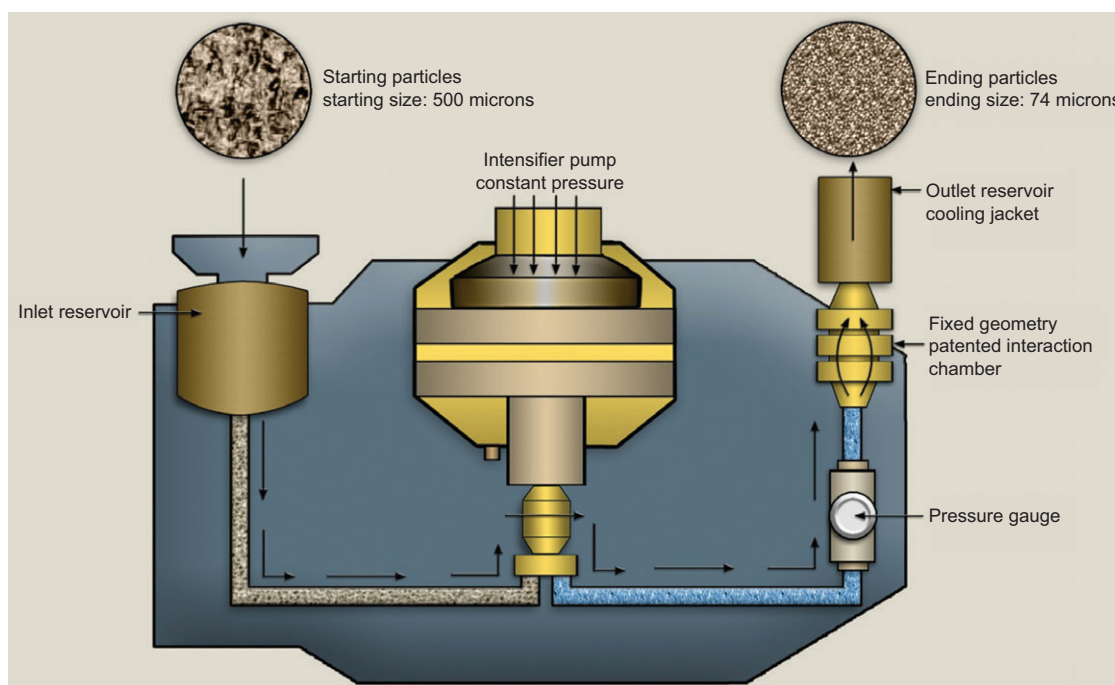
## High pressure homogenization

Oil in water nanoemulsions, containing oil portion <20%, can be prepared by this method. Anne Desrumaux and her team showed that average droplet diameters increase with increasing oil content because of the limitation on surface-active agents in the most oil concentrated emulsions due to the strong increase of the interfacial area created by the homogenising process. Moreover, the shear-thinning behavior of most oil-concentrated emulsions can

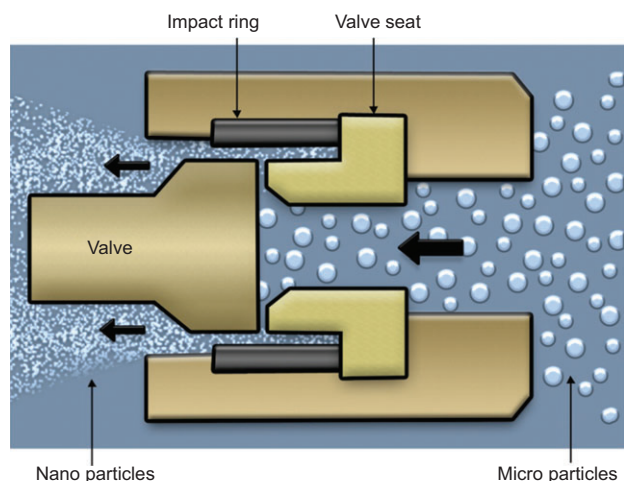
be attributed to the formation of clusters or aggregates of droplets which eventually increases droplet size. As a result, producing nano sized droplets will not be possible in case of preparing W/O nanoemulsions by high pressure homogenization method (18). Here, very high pressure is applied on the system containing oil phase, aqueous phase and the surfactant. This process is done with the help of a high pressure homogenizer (Figure 3) or piston homogenizer (2). First, the micro particles enter the valve at a relatively low velocity. The pressure is then generated by the positive-displacement pump which provides a relatively constant rate of flow. The liquid, containing micro particles, flows between the valve and seat at high velocity. As the velocity increases, the pressure decreases at the same time. The fluid is finally discharged as homogenized nanoemulsion (18).

## EIP and PIT method

The emulsion inversion point (EIP) method is a low-energy and spontaneous emulsification method. At a constant temperature, it results in diverting the intrinsic features of thermodynamically stable microemulsions or liquid crystals to be nano-structured by a progressive dilution with water or oil, respectively, for creating thermodynamically unstable but kinetically stable direct or inverse nanoemulsions. A small change in the water or oil proportion



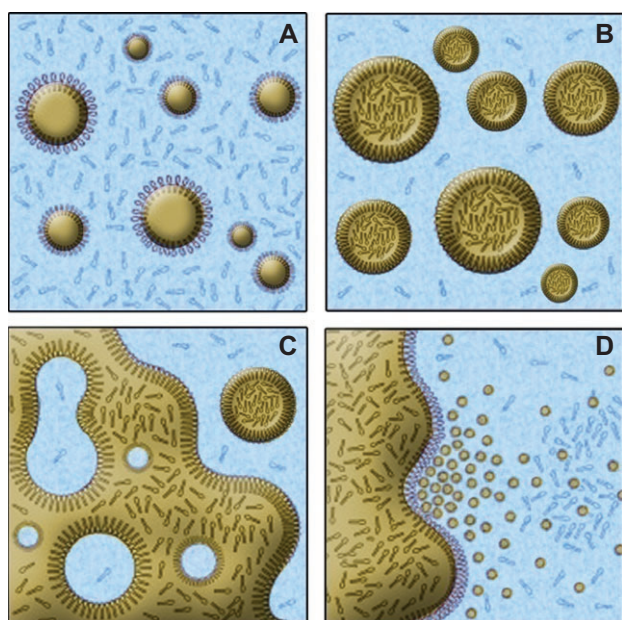
**Figure 2** Basic concept of a microfluidizer [Regenerated from (17)].



**Figure 3** High-pressure homogenizer [Regenerated from (2)].

within the established microemulsion system will change the pattern of surfactant hydration and their affinity for the aqueous phase. As a result, instabilities are created in the microemulsion system which results in its breaking up into nano-emulsion (6, 19–23).

In the phase inversion temperature (PIT) method, temperature of the emulsion system is increased to change the solubilizing pattern of the surfactant (hydrophilic to lipophilic) which forms bicontinuous microemulsions followed by emulsion inversion. The process involves four steps (Figure 4). (a) Temperature is below the PIT, it



**Figure 4** Generation of nanoemulsions using the PIT method. A water/nonionic surfactant/oil system undergoes a phase inversion [Regenerated from (24)].

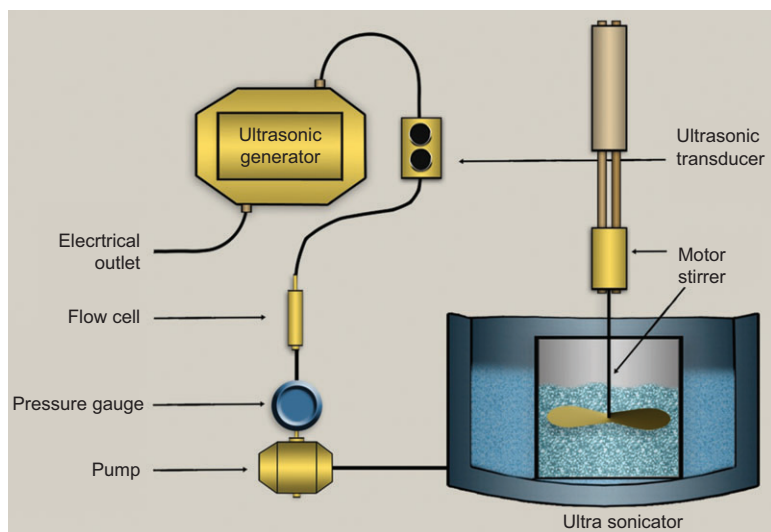
presents a macro-emulsion and the nonionic surfactants, mostly hydrophilic. (b) Temperature is increased; the surfactants gradually become lipophilic and are solubilized by the oil phase. (c) Temperature is at the PIT, bicontinuous microemulsions form. (d) Temperature is brought above the PIT, the emulsion is inverted and water is dispersed into the mixture of oil and lipophilic surfactant. The system is then cooled rapidly using water dilution, making the surfactant hydrophilic instantaneously and inducing spontaneous and rapid migration to the aqueous phase. This turbulent displacement induces the generation of nanoemulsions (24).

## Sonication

Sonication is referred to as applying ultrasound energy to agitate particles in a sample. Emulsification by ultrasonic technology mainly occurs through two mechanisms. Firstly, the use of an acoustic field produces interfacial waves which become unstable, eventually resulting in the eruption of the oil phase into the water medium in the form of droplets. Secondly, the application of low frequency ultrasound causes acoustic cavitation, that is, the formation and subsequent collapse of microbubbles by the pressure fluctuations of a simple sound wave. Each bubble collapse (an implosion on a microscopic scale) event causes extreme levels of highly localized turbulence (Figure 5). The turbulent micro-implosions act as the very effective method of breaking up the primary droplets of dispersed oil into the droplets of sub-micron size (25, 26).

## Production of nanoparticles from nanoemulsion template

Most nanoparticle formulations are effectively based on nanometric-scaled emulsions, so-called nanoemulsions. Nanoemulsified nanoparticles are mainly produced by three different methods which are high-energy method, low-energy spontaneous emulsification method and low-energy phase inversion temperature (PIT) method. The major feature of nanoemulsions which makes them prime candidates for nanoparticle engineering is their great stability of droplet suspension. Stability of an emulsion is hampered in two ways, flocculation by coalescence and Ostwald ripening. In nanoemulsion systems, flocculation is naturally prevented by steric stabilization, essentially due to the sub-micrometric droplet size. The second one is the reduction of the configurational entropy



**Figure 5** Emulsification by ultrasonic technology [Regenerated from (25)].

which occurs when inter-droplet distance becomes lower than the adsorbed layer thickness. In case of the second problem, stability is dependent on the droplet radius  $r$ , the Hamaker constant  $A$ , and the adsorbed layer thickness  $\delta$ . The stability is very high if the  $\delta/r$  value is high. In case of nanoemulsion droplets,  $\delta/r$  becomes extremely high in comparison with macroemulsions, which completely prevents its capability to coagulate (6).

## Methods of nanoparticle production from nanoemulsion template

Researchers are producing nanoparticles from different classes of drugs by nanoemulsification in order to give better pharmacological action and to ensure better drug delivery. Table 3 compiles the drugs from various classes that have been produced by nanoemulsification in recent researches which showed better results. The followings are the types of nanoparticles along with some manufacturing methods by nanoemulsification which seem to be very promising.

### Polymeric nanosphere

Polymeric nanospheres are produced by two methods which are 'in situ' polymerization and formulation with preformed polymers. Nanospheres produced by 'in situ' polymerization actually develop from the high energy nanoemulsion polymerization methods. It consists of the chemical reaction that can be described as the radical polymerization of droplets. Usually, monomers are used

as the hydrophobic phase where specific surfactants are selected for producing nanoemulsions. Thus, the nanoemulsion contains monomer droplets which are surrounded by the adsorbed surfactants. Polymerization starts among the droplets when the initiator is added in the continuous phase. In the second method, the macromolecules are dissolved in the phase to be dispersed. It involves the removal of the organic (and volatile) solvent from the formulation by evaporation or diffusion shock and therefore, polymer precipitation occurs within the organic phase template. The main difference between this method and the previous one is that the natural macromolecules, such as chitosan, polysaccharides, alginate, gelatin etc. are used here which increase their biocompatibility to reach therapeutic objectives. Secondly, nanoparticles can be produced by low-energy method in the second one (6, 27).

### Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles are defined as nano-scaled lipid matrices which are dispersed in water or in aqueous solution containing the surfactants. This type of nanoparticles seems to be a promising drug delivery system, especially for the parenteral administration. SLNs are solid at physiological temperature which are extremely biocompatible, less toxic and can protect sensitive drugs to deliver them accurately (28). High-energy production methods of SLNs involves the following steps, a) maintaining the lipid phase (plus potentially solubilized drug) 5–10°C above its melting point, b) premixing it in an aqueous surfactant solution at the same temperature, c) nanoemulsifying the

Table 3 Some preparations of nanoemulsion based nanoparticles in recent researches.

Class	Name of the drug	Materials	Types of nanoemulsion	Preparation method	Use	Research outcome	References
Antimicrobial	Carvacrol $\geq 98\%$ , d-limonene, trans-cinnamaldehyde 99%	Carvacrol $\geq 98\%$ , d-limonene, trans-cinnamaldehyde 99%, sunflower oil, essential oil, fluid soy lecithin, pea proteins, sugar ester Tween 20 and glycerol monooleate	Nanocapsule	High-pressure homogenization	Effective against several bacterial infections	Antimicrobial activity depends on the concentration of active molecule in aqueous phase	(29)
Antiarthritic	Hyaluronic acid	Hyaluronic acid-monoctearin (glycerol-monoctearate, GMS) solution, methylene chloride, Tween 80, Span 20 and CaCl <sub>2</sub>	Nanocapsule	Sonication	It works against arthritis and sores in the mouth	Better emulsion stability	(30)
Bioactive compound (Antioxidant)	Resveratrol/curcumin	Resveratrol/curcumin, soy lecithin, sugar ester, modified starch and vegetable proteins, peanut oil, palm oil and stearic acid	Nanocapsule	High-pressure homogenization	Antioxidant	Very stable emulsion preventing oxidation of the bioactive compounds	(31)
Anticancer	Polymethoxyflavone	Polymethoxyflavone, powdered b-lactoglobulin, lyso-lecithin, Tween 20, dodecyl trimethyl ammonium bromide (DTAB), glycerol (99%), ethanol (95%), Tween 85, medium chain triglyceride, corn oil, orange oil, sodium monophosphate, sodium diphosphate, hydrochloric acid (HCl) and sodium hydroxide (NaOH)	Nanocapsule	High-pressure homogenization	Used to treat cancer	Influent crystal formation in emulsion by changing emulsion type, oil type, and preparation method. Incorporation of neutral co-solvents to stabilize the emulsion	(32)
NSAID	Ibuprofen	Ibuprofen, cremophor A25 and cremophor A6, medium chain triglyceride, soybean lecithin, stearyl alcohols and sodium chloride	Lipid nanocapsule	Solvent free phase inversion method	Pain relieving	Fine nanoemulsion of 50 $\mu\text{m}$ particle size was obtained. Release rate depends on drug-lipid interaction. Increasing temperature enhances drug release rate	(33)
Antiretroviral	Ritonavir, efavirenz and lopinavir	polylactic-co-glycolic acid (PLGA) nanoparticles containing the drugs	Nanoparticle	Emulsion-solvent evaporation	Antiretroviral therapy for AIDS patients	Combination therapy which gives better and prolonged effect without causing toxicity to the macrophages. IV administration is possible	(34)
Psychoactive	Dopamine	Lipid, dopamine	Nanosphere/nanocapsule	Emulsion polymerisation	Parkinson's disease	Prevents side effects, crosses blood-brain barrier easily and target specific cells	(35)

pre-emulsion using a high-energy method (high pressure homogenizer or sonication) and finally, d) cooling it down to room temperature to crystallize the lipids. Special care has to be taken to avoid the lipid memory effect, making new crystallization possible (6).

### Nanocapsules

This is composed of colloidal objects having a shell surrounding the core structure. The core is the lipophilic solvent which acts as the liquid reservoir for drugs and the shell is made of polymers which are preferentially biodegradable, dense and rigid. Scientists have been doing extensive research on making and adapting a hydrophilic shell (6).

## Application of nanoemulsion in different drug delivery systems

Nanoemulsion is proving itself to be an effective drug delivery system overcoming the barriers confronted by the conventional methods. Various difficulties in oral, topical and other routes of drug delivery can be removed precisely by the nanoemulsification techniques. Performance of the drugs has increased in nanoemulsions with the increasing retention time. Antimicrobial drugs, as nanoemulsions, can easily penetrate through the microbial cell membrane and ensure rapid destruction of the organisms (7).

### Oral delivery

Nanoemulsion can bring a great revolution in oral drug delivery system. It has overcome several limitations of the traditional systems. Drug solubility, rate of absorption, and targeted drug delivery were always the matters of concern during designing oral dosage forms. Nanoemulsified drug delivery system has come out with a one step solution for all of these problems. In case of drug solubility, both hydrophilic and lipophilic drugs can be solubilized in either O/W or W/O nanoemulsion which in turn ensures a better dissolution because of extremely small size of the particles having both hydrophilic and lipophilic units. Furthermore, these small particles can easily penetrate through the epithelial layer to ensure good rate of absorption of the drug. Small particle size facilitates the scientists to fix and control optimum dosing which prevents dose related toxicities. Therefore, nanoemulsion has created a new opportunity

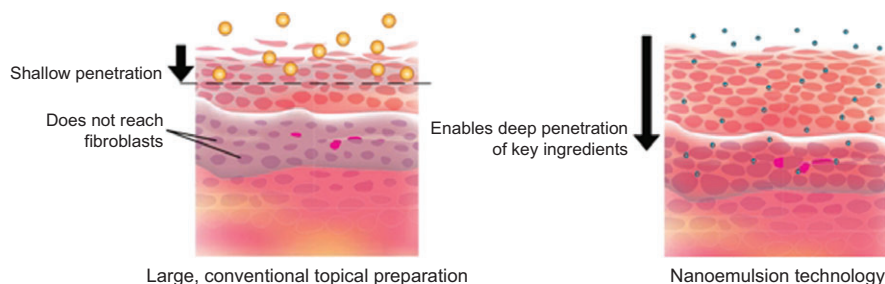
for the scientists to design poorly soluble and less bioavailable drugs in a more accurate way which could not be formulated through the conventional methods. Nanoemulsions have both hydrophilic and lipophilic units, thus different targeting moieties and drugs from various classes can be incorporated (36). These nanoemulsified drugs may even enter the cytoplasm and give more specific pharmacodynamic action inside the cell (cancer treatment). Thus it can be an ideal delivery system for drugs such as steroids, proteins, hormones, diuretic and antibiotics. Oils are effectively absorbed in the GIT through various lipid absorption mechanisms. Therefore, one of the best ways to increase the absorption of the protein drugs is to load them inside the oils so that the absorption of drugs can increase significantly along with the oil droplets (2, 36).

A recent research has been carried out in order to improve in vitro dissolution and in vivo absorption of itraconazole (ITZ), a poorly water-soluble drug, by means of novel pectin-based nanoparticles prepared from nanoemulsion templates. Nanoemulsion templates were prepared by a high-pressure homogenization method using pectin (high-methoxyl pectin HMP) as an emulsifier and chloroform as an oil phase. The in vivo absorption study in fasted rats demonstrated that pectin-based nanoparticles prepared from nanoemulsion templates could improve absorption of ITZ, which is about 1.3-fold higher than the ITZ commercial product. These findings suggested that HMP-based nanoparticles can be a promising formulation due to their high  $AUC_{0-24h}$  and  $C_{max}$  (37).

### Topical delivery

Topical drug delivery has some advantages over the oral route which include no drug loss by first pass metabolism, no damage of the drug in GI environment, no gastric irritation, no unpleasant taste or difficulty to administer and no need of disintegration and dissolution step. The main difficulty regarding topical drug delivery is the skin barrier which prevents the drug entering the systemic circulation. Nanoemulsion-based topical drug delivery can significantly overcome this barrier. Usually, drugs penetrate through the skin in three routes which are hair follicle, sweat duct and directly through the stratum corneum. The small sized nanoparticles in nanoemulsions can pass through the pores easily (Figure 6). Moreover, the hydrophobic and hydrophilic units facilitate to penetrate through the hydrophobic stratum corneum as well as the hydrophilic sweat ducts. Ropinirole, a drug with low oral bioavailability and frequent dosing, shows better penetration and greater extended release when prepared as





**Figure 6** Comparison of nanoemulsion with the conventional transdermal formulations in case of crossing skin barrier.

nanoemulsion gel. The relative bioavailability of ropin-irole was found to be enhanced more than two folds than the conventional marketed gel (38). Nanoemulsion can be used effectively against dermatitis and psoriasis (39). Positively charged nanoemulsions were found to be better penetrable and performable than the negatively charged nanoemulsions because positively charged nanoparticles interact more with the negatively charged skin to penetrate through (40, 41).

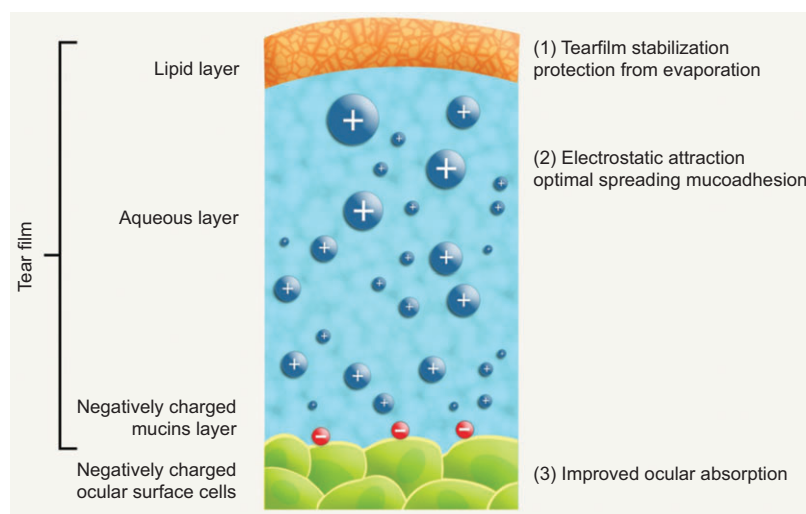
### Ophthalmic delivery

Conventional eye drops as ophthalmic drug delivery result in poor bioavailability and pharmacological action because of lacrimal secretion and nasolacrimal drainage in the eyes. Tear drainage of the eyes transports the significant part of the administered drug via the nasolacrimal duct to the gastrointestinal tract. As a result, it may be absorbed, sometimes causing side effects. The drug needs to be in contact with the eyes for a longer period of time to overcome this problem. Other preparations like ointment

or aqueous gels cause blurred vision. From this point of view, dilutable nanoemulsions are potent drug delivery for ophthalmic administration because of their numerous advantages as sustained effect and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor (42). The use of nanoemulsion as ophthalmic drug delivery also solves the problems regarding drug solubility. Cationic nanoemulsions are better vehicles for ophthalmic drug delivery since they interact with the negatively charged corneal cells and improve drug absorption (43) (Figure 7). Dorzolamide hydrochloride, a potential antiglucoma drug, was prepared as ocular nanoemulsion in an investigation and found high therapeutic efficacy and prolonged effect (42).

### Parenteral delivery

Drugs with low solubility are always considered unsuitable for parenteral administration, however, with the help of nanoemulsification techniques, they can now be formulated as parenteral dosage form. The use of biodegradable



**Figure 7** Three advantages of cationic nanoemulsions for ophthalmic delivery [Regenerated from (43)].

Table 4 Recent researches on nanoemulsion preparation from different therapeutic classes.

Class	Name of the drug	Materials	Types of nanoemulsion	Preparation method	Use	References
NSAID	Celecoxib	Celecoxib, propylene glycol mono caprylic ester, diethylene glycol monoethyl ether, glycerol triacetate (Triacetin) and acetonitrile (HPLC grade), cremophor-EL and deionizes water	Nanoemulsion	Phase Inversion	Selective COX-2 inhibitor used in the treatment of acute pain	(13)
NSAID	Aspirin	Aspirin, propylene glycol monolaurate type II, diethylene glycol monoethyl ether, carrageenan and polyoxy 35 castor oil	O/W Nanoemulsion	Sonication	Used to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication	(14)
NSAID	Flurbiprofen	Flurbiprofen, trimyristin, captex 355 EP/NF (triglycerides of caprylic and capric acid), soy phosphatidylcholine 99%, Tween 80, chloroform, methanol and water	O/W Nanoemulsion	Homogenization and sonication	Used to treat the inflammation and pain of arthritis	(15)
Antibiotic	Amoxicillin	Amoxicillin, chitosan, heparin (5000 IU/mL, MW 15 kDa, 179 IU/mg), liquid paraffin, Tween 20, Span 20, amoxicillin	W/O Nanoemulsion	Homogenization	Used against <i>H. Pylori</i>	(16)
Neutraceutical	<i>Angelica gigas</i> Nakai extract	<i>Angelica gigas</i> nakai extract, medium chain triglyceride (MCT), Tween 80 and water	O/W Nanoemulsion	Sonication	Pain relieving and combating symptoms of menopause, like hot flashes	(48)
Antitumor	Fisetin	Fisetin, Tween 80, caprylocaproyl polyoxyl-8 glycerides, lecithin, caprylic/capric triglyceride, sodium hydroxide 0.1N and sterile water for injection	Nanoemulsion	Phase inversion and sonication	Used to treat cancer	(49)
Cardiovascular	Ramipril	Ramipril, medium chain triglyceride, caprylo caproyl macrogol-8-glyceride, polyglyceryl-6-dioleate, propylene glycol mono caprylic ester, isopropyl myristate, glycerol triacetate, castor oil, Tween 80, diethylene glycol monoethyl ether, sodium perchlorate, acetonitrile and water	O/W Nanoemulsion	Phase inversion	Used in hypertension, congestive heart failure, stroke, heart attack and diabetic nephropathy	(50)
Antiemetic	Granisetron	Granisetron, egg phosphatidylcholine, isopropyl myristate, hydroxypropylmethylcellulose, hydroxypropyl- $\beta$ -cyclodextrin, polyvinylpyrrolidone, Tween 80, sodium taurocholate, lauroglycol 90, labrafil, labrafac, and poloxamer 188	Lipid nanoemulsion	Sonication	Used to treat nausea and vomiting during anticancer therapy	(51)
Antilipidemic	Ezetimibe	Ezetimibe, propylene glycol dicaprylocaprylate, caprylo caproyl macrogol-8-glyceride, propylene glycol monolaurate, propylene glycol laurate, propylene glycol monocaprylate, glyceryl monolinoleate, oleoyl macroglyceride, diethylene glycol monoethyl ether, propylene glycol mono caprylic ester, polyethoxylated castor oil, glycerol triacetate, Tween 80, Tween 20, PEG and water	O/W Nanoemulsion	-	Used against hypercholesterolaemia	(52)

(Table 4 Continued)

Class	Name of the drug	Materials	Types of nanoemulsion	Preparation method	Use	References
Antimalarial	Clotrimazole	Clotrimazole, polyethylene glycol 660 hydroxystearate, propylene glycol monocaprylate, lauryl polyoxyglycerides, hydroxypropyl methyl cellulose, HPMC 5, HPLC grade acetonitrile, buffer salts	O/W Nanoemulsion	Phase inversion	It acts against malaria infection	(53)
Antimicrobial	Cetylpyridinium chloride	Soybean oil (25%, v/v, of the total emulsion), cetylpyridinium chloride (CPC) (1%, w/v), and Triton X-100 (10%, v/v) in 65% (v/v) deionized water	O/W Nanoemulsion	Microfluidization	Anticariogenic effect	(54)
Bactericidal against <i>Mycobacterium immunogenum</i> and <i>Pseudomonas aeruginosa</i>	Mineral oil	Mineral oil, phosphate buffered saline (0.1 M at pH 7.0), mixture of polyethylene glycol p-(1,1,3,3-tetramethylbutyl)-phenyl ether, polyoxyethylated castor oil and diethylene glycol monohexyl ether (DEGHE, #32271)	Nanoemulsion	Phase inversion temperature (PIT) method	Antimicrobial action	(55)
Antihypertensive	Candesartan cilexetil	Candesartan cilexetil, soybean oil, polyoxyl-15-hydroxystearate and Tween 80	O/W Nanoemulsion	Emulsion solvent evaporation	Used to treat hypertension	(56)
Autoimmune and anti-inflammatory agent	3,5-dihydroxy-4-isopropylstilbene	3,5-dihydroxy-4-isopropylstilbene, isopropyl myristate, polyoxyethylene sorbitan fatty acid esters (Tween-80), polyoxyethylenated castor oil (EL-40), methanol, soy bean salad oil, olive oil, peanut oil and distilled water	O/W Nanoemulsion	Phase inversion temperature (PIT) method	Chronic skin diseases caused by a disorder of the autoimmune system. E.g., atopic dermatitis and psoriasis	(57)
Antiproliferative and immunosuppressive agent	Didodecyl methotrexate	Didodecyl methotrexate, phosphatidylcholine, triolein, cholesterol and cholesteryloleate	Lipid nanoemulsion	Sonication	Used in the treatment of cancer and autoimmune diseases	(58)
Antimalarial	Primaquine	Primaquine diphosphate, caprylic/capric triglyceride, egg lecithin, soyabean lecithin liquid, polyethylene-polypropylene glycol, glycerol and sorbitol	O/W Lipid nanoemulsion	High-pressure homogenization	Effective against <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> to treat malaria	(59)
Anticancer	Paclitaxel	6 mg/mL solution of paclitaxel in 527 mg of polyoxyl 35 castor oil NF, 2 mg anhydrous citric acid, and 49.7% (v/v) dehydrated alcohol, Lipoid® E80 (80% phosphatidylcholine, 8% phosphatidylethanolamine, 3.6% non-polar lipids, and about 2% sphingomyelin), ethyl alcohol and pine nut oil	O/W Nanoemulsion	Sonication	Used in the treatment of breast cancer	(60)

surfactants ensures good pharmacological action with no interference to the regular biological activities of the body. A recent research shows that Carbamazepine, a widely used anticonvulsant drug which is poorly soluble, can be prepared as nanoemulsion by spontaneous emulsification method containing 2 mg/mL where about 95% drug is released within 11 h (44). Another study shows that IV preparation of thalidomide (0.01%–0.05% w/w) by spontaneous emulsification releases 95% drug within 4 h (45).

## Nanoemulsions as nanocarrier

The principle of nanocarrier is based on the idea that extremely small size of the nanoparticles can pass through the biological barriers. Nanocarriers are polymers, amphiphilic lipids or solid colloidal particles which enclose the targeted drugs. Some examples of nanocarriers are gold nanoparticles, ceramic nanoparticles, liposomes, solid lipid nanoparticles, polymer-drug conjugates and carbon nanotubes. There are several different techniques by which drugs can be enclosed in nanoparticles. Nanocarriers are engineered in such a way as it can evade the immunological response and deliver the drug to targeted tissues (46). Nanoemulsion system can be used as a means to prepare nanocarriers for entrapping the drug. Drugs can either be entrapped in nanocarriers or bound with the surface of nanocarriers. Various emulsification methods are being used to prepare the nanocarriers. Nanocarriers can even be used very effectively to deliver the drug crossing the Blood Brain Barrier (BBB) (47).

## Recent trend in nanoemulsions

Nanoemulsions are recently being prepared and trialed for a number of critical disorders and limitations related to drug therapy. They are gradually making a revolution in increasing drug permeation and bioavailability. Mendes and his team have recently shown that lecoregional injection of lipid nanoemulsion concentrates more in breast

carcinoma minimizing interaction with the healthy cells. Therefore, it can be a promising approach for drug-targeting in neoadjuvant chemotherapy in breast cancer treatment (10). Hyun-Jong Choc and co-workers observed that a novel lipid nanoemulsion system could improve permeation of granisetron. One of their formulations showed 2.78 times higher drug permeation by nanoemulsion than conventional GRN powder (48). A research team, led by Guy G. Chabot, demonstrated that nanoemulsion formulation of fisetin improves its bioavailability and antitumour activity in mice (49). In recent years nanoemulsion has become a promising tool to improve bioavailability of several drugs along with nanosuspension and other various solubility enhancement techniques (61). Recent research on nanoemulsion preparation from various therapeutic classes has been summarized in Table 4.

## Conclusion

Nanoemulsion has already gained much attention in the recent researches of pharmaceutical sciences because of overcoming limitations of many conventional drug therapies and for being more stable than other emulsion systems. Many drugs are presently being trialed to be formulated as nanoemulsions. Different methods of nanoemulsion preparation give the scientists a wide range of choice. Nanocarriers, nanoparticles, and nanocapsules are also being formulated based on nanoemulsification techniques. The difficulty of penetrating physiological membranes is greatly being removed by the application of nanoemulsions. There are many possibilities to design many drugs based on nanoemulsification that would dramatically reduce the drug dosage, deliver the drug to the right place, increase the local concentration of the drug, and minimize the side effects. Nanoemulsions are actually breaking down the frontiers in designing more specific and targeted drug delivery. So, it is becoming an excellent choice of formulation and has opened a new era in the field of drug therapy.

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Kumar Bishwajit Sutradhar Studied Pharmaceutical Technology in his MSc at the University of Asia Pacific (2010) and joined Stamford University Bangladesh in the Department of Pharmacy in 2011. His work is focused on method development and validation, polymer chemistry and formulation and development of pharmaceutical dosage forms using different natural polymers available in Bangladesh. His current research activities include developing alternative method for tri-layer tablets with release modifiers and nanoparticles for better topical preparations. He is working as an Editor in Stamford Journal of Pharmaceutical Sciences (SJPS) and also teaches Formulation Technology and Pharmaceutics at Stamford University Bangladesh.



Md. Lutful Amin has completed his Bachelor of Pharmacy (B.Pharm) degree from Stamford University Bangladesh. He has conducted several research works on drug delivery systems. At present he is doing his project on mucoadhesive microsphere. He is also doing various pharmaceutical researches along with the faculty members of the university. The author is enthusiastic particularly in drug delivery systems. He has enormous curiosity in nanotechnology and its diversified applications in pharmaceutical sciences.