Review Article

Nanoemulsion: A brief review on development and application in Parenteral Drug Delivery

Tushar Hemant Nikam, Mahesh Pralhad Patil, Snehal Sunil Patil, Gautam P. Vadnere, Santram Lodhi*

Department of Pharmacognosy,

Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda Dist. Jalgaon (Maharashtra) 425107 India.

Received: 22 March 2018 Revised: 20 April 2018 Accepted: 10 May 2018

Abstract

An advanced mode of drug delivery system has been developed to overcome the major drawbacks associated with conventional drug delivery systems. This review gives a detailed idea about a nanoemulsion system. Nanoemulsions are nano-sized emulsions, which are manufactured for improving the delivery of active pharmaceutical ingredients. These are the thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, i.e., surfactant and co-surfactant. The droplet size of nanoemulsion falls typically in the range 20–200 nm. Nanoemulsions are biphasic dispersion of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic surfactant. These come across as ultrafine dispersions whose differential drug loading; viscoelastic as well as visual properties can cater to a wide range of functionalities including drug delivery. However there is still relatively narrow in sight regarding development, manufacturing, fabrication and manipulation of nanoemulsions which primarily stems from the fact that conventional aspects of emulsion formation and stabilization only partially apply to nanoemulsions. This general deficiency sets up the premise for current review. We attempt to explore varying intricacies, excipients, manufacturing techniques and their underlying principles, production conditions, structural dynamics, prevalent destabilization mechanisms, and drug delivery applications of nanoemulsions to spike interest of those contemplating a foray in this field.

Keywords: Nanoemulsions, amphiphilic surfactant, water in oil (W/O), oil in water (O/W)

Introduction

Perspective drug delivery systems can be defined as mechanisms to introduce therapeutic agents into the body. Chewing leaves and roots of medical plants and inhalation of soot from the burning of medical substances are examples of drug delivery from the earliest times. However, these primitive approaches of delivering drugs lacked a very basic need in drug delivery; that is, consistency and uniformity (a required drug dose). This led to the development of different drug delivery methods in the later part of the eighteenth and early nineteenth century. Those methods included pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions, suspension, cachets, troches, lozenges, nebulizers, and many other traditional delivery mechanisms. Many of these delivery mechanisms use the drugs derived from plant extracts (Paolino and Webster, 2006). As the technological advancements been made some new formulation approaches have been devised by the scientists. Most of the new chemical entities being invented pose the problem of poor solubility. Nanotechnology and nanoscience are widely seen as having a great potential to bring benefits to many areas of research and applications where poor solubility is an issue with API.

Nanoemulsions are a colloidal particulate system in the submicron size range acting as carriers of drug molecules.

**Address for Corresponding Author:*
Dr. Santram Lodhi
Department of Pharmacognosy,
Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda Dist. Jalgaon (Maharashtra) 425107 India.
Email: srlodhi78@gmail.com

DOI: https://doi.org/10.31024/apj.2018.3.2.2

Their size varies from 10 to 1,000 nm. These carriers are solid spheres and their surface is amorphous and lipophilic with a negative charge. Magnetic nanoparticles can be used to enhance site specificity. As a drug delivery system they enhance the therapeutic efficacy of the drug and minimize adverse effect and toxic reactions. Major application includes treatment of infection of the reticuloendothelial system (RES), enzyme replacement therapy in the liver, treatment of cancer, and vaccination. An emulsion is a biphasic system in which one phase is intimately dispersed in the other phase in the form of minute droplets ranging in diameter from 0.1 to 100 lm. It is a thermodynamically unstable system, which can be stabilized by the presence of an emulsifying agent (emulgent or emulsifier). The dispersed phase is also known as internal phase or the discontinuous phase while the outer phase is called dispersion medium, external phase or continuous phase. The emulsifying agent is also known as intermediate or inter phase. The term 'nanoemulsion' also refers to a miniemulsion which is fine oil/water or water/oil dispersion stabilized by an interfacial film of surfactant molecule having droplet size range 20–600 nm. Because of small size, nanoemulsions are transparent. There are three types of nanoemulsion which can be formed:

a) Oil in water nanoemulsion in which oil is dispersed in the continuous aqueous phase,

b) Water in oil nanoemulsion in which water droplets are dispersed in continuous oil phase, and

c) Bi- continuous nanoemulsions

Techniques of Nanoemulsions Preparation (Pershing et al., 1993)

Nanoemulsions have very small particle size range; they can be most effectively produced using high-pressure equipment. The most commonly used methods for producing nanoemulsions are High-pressure homogenization and Microfluidization used at both laboratory and industrial scale. Other methods like. Ultrasonification and In-situ emulsification are also suitable for preparation of nanoemulsion.

1. High-Pressure Homogenization

The preparation of nanoemulsions requires high- pressure homogenization. This technique makes use of high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1nm). The dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion .The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids. This technique has great efficiency, the only disadvantage being high energy consumption and increase in temperature of emulsion during processing.

To obtain the optimized formulation following process variables should be investigated:

Effect of Homogenization Pressure: It is optimized the process parameter ranging from 100 to 150 bars. The higher is the size the lower is the particle size obtained e.g., RMRP 22.

No. of Homogenization cycles: The higher the homogenization cycles the smaller is the particle size obtained. The cycles are carried out in 3, 4 or 10 cycles. The number of cycles is analysed by poly disparity index of drug after each cycle.

Advantages

- Ease of scale-up and little batch-to-batch variation.
- Narrow size distribution of the nanoparticulate drug.
- Flexibility in handling the drug quality.
- Effectively used for thermolabile substances.

2. Microfluidization (Hadgraft, 2001)

Micro-fluidization is a mixing technique, which makes use of a device called micro-fluidizer. This device uses a high-pressure positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called „micro-channels". The product flows through the micro channels on to an impingement area resulting in very fine particles of sub-micron range.

The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is into a micro-fluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber micro-fluidizer repeatedly until desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion.

3. Ultrasonication (Bhatt and Madgav, 2011)

The preparation of Nanoemulsion is reported in various research papers which aim to use the ultrasonic sound frequency for the reduction of the droplet size. Another approach is the use of a constant amplitude sonotrode at system pressures in excess of the ambient value. It is well known that increasing the external pressure increases the

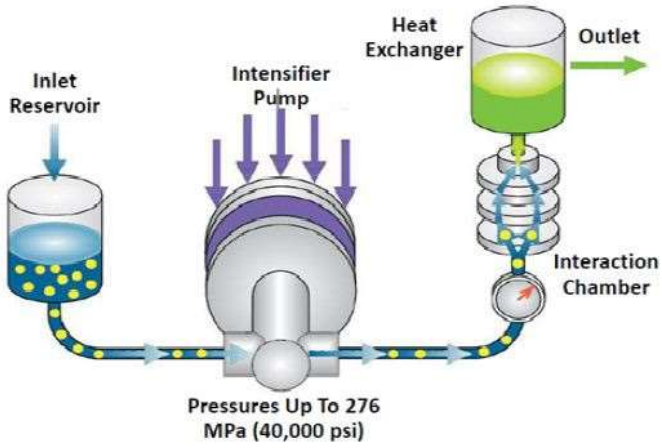

Figure 1. Micro-fluidization **(**Hadgraft, 2001**)**

cavitations threshold within an ultrasonic field and thus fewer bubbles form. However, increasing the external pressure also increases the collapse pressure of cavitations bubbles. This means that the collapse of the bubbles when cavitation occurs becomes stronger and more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a low frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to optimum level.

4. Phase inversion method (Hussan, 2011)

In this method, fine dispersion is obtained by chemical energy resulting of phase transitions produced by emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping temperature constant or vice versa. The phase inversion temperature was first done by it was concluded that increase in temperature results in the chemical changes of polyoxyethelene surfactants by degradation of the polymer chain with the temperature.

5. Spontaneous Emulsification (Devarajan and Ravichandran, 2011)

It involves three main steps

a) Preparation of homogeneous organic solution composed of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant.

b) The organic phase was injected in the aqueous phase under magnetic stirring the o/w emulsion was formed.

c) The water-miscible solvent was removed by evaporation under reduced pressure.

6. Solvent Evaporation Technique (Shah and Bhalodia, 2010)

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

7. Hydrogel Method

It is similar to solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevent crystal growth and Ostwald ripening.

Formulation aspects and method of preparation of nanoemulsion

Formulation of nanoemulsion includes active drug, additive and emulsifier. The various methods for the preparation of nanoemulsion include two methods: **(a)** high-energy emulsification and **(b)** low-energy emulsification. The high-energy emulsification method includes high-energy stirring, ultrasonic emulsification, high-pressure homogenization, micro-fluidization, and membrane emulsification (Tiwari and Amiji, 2006; Perdiguer et al., 1997; Banker et al., 2002). The low-energy emulsification method includes phase inversion temperature, emulsion inversion point, and spontaneous emulsification (Ahuja et al., 2008). Using a combined method, which includes the high-energy and low-energy emulsification, it is possible to prepare reverse nanoemulsion in a highly viscous system.

The amount of surfactant required for micelle formation can be roughly estimated by assuming an equilibrium surface density, ρs, for surfactant molecules on the droplet interfaces. Once nanoemulsions have been formed, it is possible to manipulate them in a variety of useful ways. Poly-disperse nanoemulsions can be separated by size into several more mono-disperse nanoemulsions in a process known as fractionation. A kinetic stability that lasts for months, stability against dilution or even against temperature changes, totally unlike the (thermodynamically stable) micro-emulsions. (Anton and Saulnier, 2008) Emulsions are thermodynamically unstable systems, due to the free energy of emulsion formation (ΔGf) greater than zero. The large positive interfacial energy term ($\lambda\Delta A$) outweighs the entropy of droplet formation ($T\Delta Sf$), also positive. The terms λ and ΔA respectively represent the surface tension and the surface area gained with emulsification. Emulsion instability is therefore induced by the positive sign of ΔGf (Equation 1).

$$\Delta Gf = g\Delta A - T\Delta Sf$$

Destabilization of emulsions is associated with its natural

tendency towards a minimal interfacial area between the two immiscible phases which can be achieved by two mechanisms: (i) Flocculation followed mostly by coalescence, and (ii) Ostwald ripening. In nano-emulsion systems, flocculation is naturally prevented by steric stabilization, essentially due to the sub-micrometric droplet size. In short, when interfacial droplet layers overlap, steric repulsion occurs, from two main origins (Anton and Saulnier, 2008; Napper, 1983; Kahlweit, 1982). The first one is the unfavorable mixing of the stabilizing chain of the adsorbed layer, depending on the interfacial density, interfacial layer thickness δ, and Flory–Huggins parameter χ (which reflects the interactions between the interfacial layer and solvent). The second one is the reduction of the configurationally entropy, due to the bending stress of the chains, which occurs when inter-droplet distance h becomes lower than δ. Decrease of free energy will result in the decrease of the interfacial area due to which larger dispersed droplets forms from the smaller ones, owing to the higher solubility in the bulk of the smaller droplets which is known as Ostwald ripening and it will increase throughout the process (Kahlweit, 1982). In processes involved in nanoparticle engineering, i.e., for multi component emulsion droplets by adding monomer, polymer, or simply surfactant or co-surfactant, the above approximation is surpassed. The rate of ripening can be reduced by several orders of magnitude when the additive has a substantially lower solubility in the bulk phase than the main component of the droplet. This phenomenon has been widely studied (Anton and Saulnier, 2008; Higuchi and Misra, 1962; Smith and Davis, 1973) since it appears to be an efficient method to reduce the Ostwald ripening rate, even when using small amounts of additives. In short, it is explained by the difference of solubility in the continuous phase between the dispersed phase noted (Paolino and Webster, 2006) and the additive less soluble in this example. The first step remains similar to the ripening without additives, since only the component diffuses from the smaller to the larger droplets, due to the higher chemical potential of the materials within the smaller drops. Gradually, the chemical potential in the larger droplets increases due to the presence of the component. Until the diffusion process of is stopped. Equilibrium is reached between the two opposing effects and the limiting process becomes the diffusion of the less soluble additive significantly reducing the ripening rate and the nanoemulsion destabilization. Ostwald ripening is a diffusion-controlled process, but this assumption does not take into account the fact that surfactants, polymeric emulsifiers or stabilizers can create a thick steric barrier at the droplet interface which reduced inner diffusion rate (Smith and Davis, 1973; Bus call et al., 1979).

Components of Nanoemulsion

The main components of nanoemulsion are oil, emulsifying agents, and aqueous phases (Gasco et al., 1991; Kriwet and Goymann, 1995; Trotta, 1999). Oils can be of any type like castor oil, corn oil, coconut oil, evening primrose oil, linseed oil, mineral oil, olive oil, peanut oil, etc. A mixture of oil and water may yield a crude temporary emulsion, which upon standing, will separate in two distinct phases due to the coalescence of the dispersed globules. Emulgents or emulsifying agents can impart stability to such systems. Emulgents are broadly classified as surfactants like spans and tweens, hydrophilic colloids such as acacia and finely divided solids, e.g., bentonite and veegum. An emulgent in addition to its emulsifying properties, Should be nontoxic and its taste, odour and chemical stability should be compatible with the product. Some of the desirable properties of an emulgent are: (1) it should be able to reduce the surface tension to below 10 dynes/cm, (2) it should be adsorbed rapidly around dispersed phase globule to form a complete and coherent film to prevent coalescence, (3) it

Table 1. Formulation ingredients of Nanoemulsion

Components	Examples
Oils	Castor oil, Corn oil, Coconut oil, Evening primrose oil, linseed oil, Mineral oil, olive oil, peanut oil
Emulgent	Natural lecithins from plant or animal source, phospholipids, castor oil. Derivatives, polysorbates, sterylamine
Surfactant	Polysorbate20, Polysorbate80, Polyoxy-60, castor oil, Sorbitan mono oleate, PEG300, Caprylic glyceride
Co- Surfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer
Tonicity modifiers	Glycerol, Sorbitol and xylitol
Additives	Lower alcohol (ethanol), propylene glycol, 1, 3-butylenes glycol, sugars such as butylenes glycol, sugars such as glucose, sucrose, fructose, and maltose
Antioxidants	Ascorbic acid and tocopherol

should help in building up an adequate zeta potential and viscosity in the system so as to impart optimum stability, and (4) it should be effective in a fairly low concentration. Emulgents form monomolecular, multimolecular or particulate films around the dispersed globules.

Monomolecular films

Surfactant type of emulgents stabilizes a nanoemulsion by forming a monolayer of adsorbed molecules or ions at the interface reducing interfacial tension. In modern day practice, combination of emulgents is preferred over single emulgent. The combination consists of a predominantly hydrophilic emulgent in the aqueous phase and a hydrophobic agent in the oily phase to form a complex film at the interface.

Multimolecular films

Hydrated lyophilic colloids form multimolecular films around globules of dispersed oil. Hydrated colloids do not cause any appreciable lowering of surface tension and their ability to form strong, coherent multimolecular films. Their tendency to increase the viscosity of the continuous phase enhances the stability of emulsion.

Solid particulate films

The emulgents forming particulate films are small solid particles that are wetted to some degree by both aqueous and non-aqueous liquid phases. They are concentrated at the interface where they produce a film around the dispersed globules thus preventing coalescence.

Table 2. List of oils used in Nanoemulsion

Name of oil	Chemical Name	Manufacture
Captex 355	Glyceryl Tricaorylate/Caprate	Abitec
Captex 200	Propylene Dicaprylate/Dicaprate Glycol	Abitec
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)	Abitec
Witpsol	90:10%w/w c12 Glyceridetri:diesters	Sasol pharmaceutical excipient
Myritol 318	C8/c10 triglycerides	Russia
Isopropyl myristate	Myristic acid isopropyl ester	Fluka

Table 3. List of adsorption enhancers

S. No.	Solubilizing, surfactants, emulsifying agents adsorption enhancers.
1	Capryol 90
2	Gelucire 44/14,50/13
3	Cremophor RH 40
4	Imwitor 191,308(1),380,742,780 K,928,988
5	Labrafil M 1944 CS,M 2125 CS
6	Lauroglycol 90
7	PEG MW > 400
8	Plurol oleique CC 497
9	Poloxamer 124 & 188
10	Softigen 701, 767
11	Tagat TO
12	Tween 8

Factors affecting the Formulation of Nanoemulsion (Kim et al., 1992**)**

a) Appropriate composition is required to avoid Oswald ripening the dispersed phase should be highly insoluble in the dispersed medium.

b) The surfactant is an essential part of the Nanoemulsion. They should not form lyotropic liquid crystalline "microemulsion" phases. Systems containing short chain alkanes, alcohols, water, and surfactants form the phases which are generally used with the co surfactant.

c) The presence of excess surfactants enables new surface area of nanoscale to be rapidly coated during emulsification there by inhibiting induced coalescence.

d) Extreme share must be applied to rupture microscale droplets to nanoscale by providing the stress level to reach above the Laplace pressure of the droplets with a pressure of 10- 100 atm. Out of various methods ultrasonication is widely used in laboratory.

Characterization of Nanoemulsion

The unique qualities and performance of nanoparticles as devices of drug delivery arise directly from their physicochemical properties. Hence, it is keen to understand and determine them to characterize its behavior. A good understanding allows prediction of *in vivo* performance as well as allowing particle design, formulation development, and process troubleshooting to be carried out in a rational fashion (Haskell, 2012). It will includes characteristics such as thermodynamic stability testing. (Shinha and Ganesh, 2015; Tadros, 2004; Guglielmini, 2008; Tadros, 1982) Dilution stability transmittance measurement, Globule size distribution. Zeta potential and *in vitro* assay. Apart from that it should be evaluated for pH, conductivity, refractive index etc. (Pershing et al., 1993).

The droplet size, viscosity, density, turbidity, refractive

index, phase separation and pH measurements shall be performed to characterize the Nanoemulsion. The droplet size distribution of Nanoemulsion vesicles can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting Nanoemulsion stability.

1. Dye Solubilisation

A water soluble dye is solubilized within the aqueous phase of the W/O globule but is dispersible in the O/W globule. An oil soluble dye is solubilized within the oil phase of the O/W globule but is dispersible in the W/O globule.

2. Dilutability Test

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

3. Conductance Measurement

O/W Nanoemulsion where the external phase is water, are highly conducting whereas W/O are not, since water is the internal or dispersal phase. To determine the nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful. A sharp increase in conductivity in certain W/O Nanoemulsion systems was observed at low volume fractions and such behaviour was interpreted as an indication of a „ percolative behaviour" or exchange of ions between droplets before the formation of bicontinuous structures. Dielectric measurements are a powerful means of probing both structural and dynamic features of Nanoemulsion systems.

4. Dynamic Light-Scattering measurements (Tanojo et al., 1997)

The DLS measurements are taken at 90° in a dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm. The data processing is done in the built-in computer with the instrument.

5. Polydispersity

The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 25oC using a He-Ne laser.

6. Phase Analysis

To determine the type if Nanoemulsion that has formed the phase system (O/W or W/O) of the Nanoemulsions is determined by measuring the electrical conductivity using a conductometer.

7. Interfacial Tension (Leong et al., 2009)

The formation and the properties of Nanoemulsion can be studied by measuring the interfacial tension. Ultra low values of interfacial tension are correlated with phase behaviour, particularly the existence of surfactant phase or middle-phase Nanoemulsions in equilibrium with aqueous and oil phases.

Spinning-drop apparatus can be used to measure the ultra low interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.

8. Viscosity measurement

Temperatures using Brookfield type rotary viscometer. The sample room of the instrument The viscosity of Nanoemulsions of several compositions can be measured at different shear rates at different must be maintained at 37±0.2°C by a thermo bath, and the samples for the measurement are to be immersed in it before testing.

9. pH

The apparent pH of the formulation was measured by pH meter.

10. Refractive Index (Aubrun et al., 2004)

The refractive index, n, of a medium is defined as the ration f the speed, c, of a wave such as light or sound in a reference medium to the phase speed, vp, of the wave in the medium. n=c/vp; It was determined using an Abbes type refractrometer (Nirmal International) at 25±0.5°C.

11. Transmission Electron Microscopy (TEM)

Morphology and structure of the nanoemulsion were studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of nanoemulsion droplets. Observations was performed as, a drop of the nanoemulsion was directly deposited on the holey film grid and observed after drying.

***12. In Vitro* Skin Permeation Studies** (Nicolosi et al., 2008)

In vitro skin permeation studies were performed by using Keshary Chien-diffusion cell. It was performed on abdominal skins and was obtained from male rats weighing 250±10 gm with are circulating water bath and 12 diffusion cells. The skins were placed between the donor and the receiver chambers of vertical diffusion cells. The receiver chambers were filled with freshly water containing 20% ethanol. The receiver chambers were set at 37oC and the solution in the receiver chambers was stirred continuously at 300 rpm. The formulations were placed in the donor chamber. At 2, 4, 6, 8 h, 0.5 ml of the solution in the receiver chamber was removed for GC analysis and replaced

immediately with an equal volume of fresh solution. Each sample was performed three times 7. The cumulative corrections were made to obtain the total amounts of drugs permeated at each time interval. The cumulative amounts of drug permeated through rat skins were plotted as a function of time. The permeation rates of drug at a steady-state through rat skins were calculated from the slope of linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot.

13. Thermodynamic Stability Studies (Kazimiera et al., 2009)

During the thermodynamic stability of drug loaded Nano-emulsions following stress tests as reported:

- **Heating Cooling Cycle:** Nanoemulsion formulations were subjected to six cycles between refrigerator temperature (4°C) and 45°C. Stable formulations were then subjected to centrifugation test.
- **Centrifugation:** Nanoemulsion formulations were centrifuged at 3500 rpm and those that did not show any phase separation were taken for the freeze thaw stress test.
- **Freeze Thaw Cycle:** In this the formulation were subjected to three freeze thaw cycles between 21°C and +25°C kept under standard laboratory conditions. These studies were performed for the period of 3 months.

Bioavailability of Nanoemulsion

Kinetics of drug release

Variety of stimuli, including pH, temperature change, enzyme activity and ionic strength of the surrounding media can trigger drug release from nanoemulsion droplet. Release of drug from nanoemulsion in passive cases is dictated by Fick's first law and is given by the following equation (Capek, 2004).

$t_{1/2} = 0.0585r^2K_{ow}/D$

here (t1/2) is the time required for half of drug to diffuse out of oil, r is droplet radii, D is the diffusion coefficient of drug (an intrinsic property) and Know is oil water partition coefficient. Very lipophilic drugs may only be released when lipid or oily components have been digested away. A no emulsions however have very high oil water interfacial area in comparison to traditional emulsions and are therefore expected to be digested more rapidly. Small droplet radius of nanoemulsion also implies that diffusion times of drug across oil may be fairly rapid. Consequently, nanoemulsions are sometimes fixed in a structured vehicle such as organogel to provide a tortuous pathway delaying drug release (Huang, 2012). Another technique for controlling drug release is coating of nanoemulsions by rigid and thick layers of polymer, to form layer bilayer nanocapsules using emulsion as a decorative template (Asthna et al., 2013). Surfactants also modulate drug release kinetics. A tightly packed interfacial layer can serve as a barrier turning nanoemulsion into a nanoreservoir, and can act as principal rate controlling mechanism.

Applications of Nanoemulsions in Parenteral Drug Delivery (Kemken et al., 1992)

Nanoemulsion are advantages for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. fats, carbohydrates, vitamins etc. Nanoemulsions of natural oils (soyabean, sesame and olive) with the non toxic

Table 4. Examples of parenteral Nanoemulsions

Drugs	Disperesed Phase	Surfactant	Purpose
Carbamazepine	Castor oil, MCT	Soy lecithin, Polyoxyl 35, castor oil, Tween 80	Overcome poor solubility
Thalidomide	Castor oil, olive oil, soyabean oil MCT	Twee 80	Overcome poor solubility
Docetaxel	Oleic acid, Stearyl amine	Egg lecithin	Poor solubility, hydrolytic instability, and drug-induced side effects
Primaquine	Miglylol 812	Pluronic F68	Dose reduction, improved bioavailability, reduced toxicity
Fisetin	Miglylol 812, soybean oil, ethyl oleate	Labrasol, Lipoid E80	Improved pharmacokinetics and anti- tumor activity
Insulin	Self assembling protein complex	Poly vinyl alcohol	Protection against enzymatic degradation
Clotrimazole	Soybean oil	Pluronic F68, cremophor, Tween 20, tween 80	Increased bioavailability
Paclitaxel and ceramide	Pine nut oil	Lipoid-80	Increased cell uptake
Paclitaxel and Sulforhodamine B	Vitamin E	TPGS	Long circulation half lives increase theranostic capability

surfactant Pluronic F-68 via ultrasound for parentral feeding. Lipid nanoemulsion has been widely explored for parentral delivery of drugs. Nanoemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle Nanoemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O Nanoemulsion can be used for parenteral delivery.

Parenteral nanoemulsions have varying applications. They are used to deliver drugs with lower bioavailability and/or narrow therapeutic indices. Chlorambucil, a lipophilic anticancer agent has been administered parenterally as a nanoemulsion (fabricated using ultrasonication and high pressure homogenization method) for treatment of ovarian and breast carcinoma (Singh et al., 2015). Tagne et al. have developed a water soluble nanoemulsion of tamoxifen to increase its effectiveness in breast cancer (Ganta et al., 2010; Monteagudo et al., 2012) TOCOSOL™ a vitamin E nanoemulsion containing paclitaxel was formulated using high pressure homogenization for treatment of various cancers like ovarian cancer, breast cancer etc. It was hypothesized that TOCOSOL™ would reduce toxic side effects of paclitaxel and it had shown great initial merit against metastatic breast cancer but unfortunately its Phase 3 trials did not meet primary endpoint (Bawa et al., 2016). This however, has not hindered further preclinical deliberations with TOCOSOL™ or undermined its formulation attributes like ultrafine (40–80 nm), neutral and stable droplets. TOCOSOL™ produces greater tumor suppression than plain drug in colon adenocarcinoma model solution and therefore warrants further exploration (Bawa et al., 2016). Taking note, our group has also attempted a slightly altered Vitamin E nanoemulsion of paclitaxel to accentuate inherent anti-proliferative and immune therapeutic activity of Vitamin E. We found that drug loaded nanoemulsion substantially enhanced anticancer activity of paclitaxel by opening up alternative pathways of mitochondrial killing, pharmacokinetic improvement, and immune modulation. Overall safety (measured by serum markers and organ histology) was also improved (Pawar et al., 2014). O/W parenteral lipid nanoemulsion of diclofenac has been investigated for treatment of arthritic conditions. Nanoemulsion containing diclofenac with mean droplet size of 200 nm was prepared by high pressure homogenization and ultrasonication. It was observed in vivo that diclofenac nanoemulsion provided sustained drug release allowing substantial dose reduction (Ramreddy et al., 2012). Nanoemulsions can be converted into stealth/ long circulating nanoemulsions by coating or attaching a hydrophilic moiety such as PEG on to their surface which prevents identification, opsonisation and uptake by mononuclear phagocyte system (MPS). This can be exploited in targeting tumors by enhanced permeability and retention effect. For instance Hak et al. surface coated multifunctional nanoemulsions with PEG for its successful intravenous delivery (Hak et al., 2012). They utilized paramagnetic and fluorescent lipids (for multimodal detection and imaging) to formulate nanodroplets which were then coated with a targeting ligand, RGD peptide, and PEG. It was assumed that PEG coating would prevent MPS uptake allowing preferential accumulation of nanoemulsion in tumor microenvironment, whereas RGD peptide would facilitate interaction of droplets with Rvβ3-integrin receptor present on tumor surface. For targeting diseases, which harbour pathogens inside macrophages like tuberculosis, leishmaniasis, MPS needs to be penetrated, pretty much contrary to principle of stealth nanoemulsions. Developed a layer by layer polyelectrolyte coated nanoemulsion bearing doxorubicin for intervention in visceral leishmaniasis (caused by a parasite which resides in MPS). They utilized phosphatidyl serine as a targeting ligand. It was found that phosphatidyl serine coated nanoemulsion was taken up massively by macrophages allowing selective payload delivery in deep (normally inaccessible) residence site of parasite (Kansal et al., 2012). Our group has also utilized a similar strategy to deliver amphotericin B to an intra-macrophage location via an O/ W nanoemulsion template decorated with chitosan. Toxicity studies in macrophage amastigote system and efficacy study in infected hamsters suggested that developed nanoemulsion exceeded performance of marketed product (Fungi zone) to augment antileishmanial property of amphotericin (Asthana et al., 2013). Nanoemulsion approach has been used to tackle drug resistance either by employing smart excipients like TPGS, or by using multi drug systems which potentiate primary anti-cancer entity. For instance have co administered paclitaxel and curcumin via a nanoemulsion to overcome drug resistance in ovarian cancer cells SKOV3. Efficacy of delivery system was established by quantitative cellular uptake studies (Ganta and Amiji, 2009). Another group has developed a core matched nanoemulsion using vitamin E and TPGS to co-deliver hydrophilic and hydrophobic cytotoxics, 5- fluoroucacil and paclitaxel, to overcome drug resistance in human epidermal carcinoma cell line KB- 8-5 (Y. Ma et al., 2014). A vitamin E derivatives nanoemulsion carrying paclitaxel has been developed to tackle intrinsic or acquired drug resistance in ovarian carcinoma by inhibiting P-gp and altering levels of apoptotic and anti-apoptotic proteins, Bax and Bcl-2. Baicalein, a multidrug resistance reversal agent, has been co delivered with paclitaxel using a nanoemulsion platform to improve its in vitro cytotoxicity,

cellular uptake and apoptosis (Meng et al., 2016). Recently, 'high intensity focused ultrasound-responsive perfluorocarbon nanoemulsions' have emerged as a new class of smart multifunctional vehicles which exhibit theranostic properties and release their payload in a controlled manner (Mura et al., 2013). Perfluorocarbons are fluorinated liquids which include perfluoropentane, perfluorohexane perfluorodecalin, perfluorooctyl bromide, perfluorotributylamine, perfluoro-15-crown-5-ether and were used mainly for liquid ventilation (Zhou et al., 2014). However fluorine-19 isotope in these fluorinated carbons enables quantitative fluorine-19 magnetic resonance imaging (Kislukhin et al., 2016). When stimulated ultrasonically these volatile compounds vaporize, transforming the nanoemulsion system into high-contrast microbubbles that cause drug release. There have been several studies detailing effect of acoustic and formulation parameterson contrast and effect provided by the droplets. In one such study synthesized perfluorohexane/alginate nanoemulsion (average size 55 nm) for co delivery of doxorubicin and curcumin to overcome multi drug resistant cancer. It was found that ultrasound irradiation significantly increased combinatorial cytotoxicity and in vivo tumor regression of doxorubicin and curcumin loaded perfluorocarbon nanoemulsion in comparison to pure drugs (Baghbani and Moztarzadeh, 2017). In another effort have formulated a paclitaxel-loaded perfluorocarbon nanoemulsion and obtained efficient tumor reversion in breast, ovarian, and pancreatic murine models under the influence of ultrasound (Rapoport, et al., 2009).

Summary and conclusion

An advanced mode of drug delivery system has been developed to overcome the major drawbacks associated with conventional drug delivery systems. This review gives a detailed idea about a nanoemulsion system. Nanoemulsions are nano-sized emulsions, which are manufactured for improving the delivery of active pharmaceutical ingredients. These are the thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, i.e., surfactant and co-surfactant. The droplet size of nanoemulsion falls typically in the range 20–200 nm. The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase. In this review, the attention is focused to give a basic idea about its formulation, method of preparation, characterization techniques, evaluation parameters, and various applications of nanoemulsion.

Nanoemulsions are biphasic dispersion of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic surfactant. These come across as ultrafine dispersions whose differential drug loading; viscoelastic as well as visual properties can cater to a wide range of functionalities including drug delivery. However there is still relatively narrow insight regarding development, manufacturing, fabrication and manipulation of nanoemulsions which primarily stems from the fact that conventional aspects of emulsion formation and stabilization only partially apply to nanoemulsions. This general deficiency sets up the premise for current review. We attempt to explore varying intricacies, excipients, manufacturing techniques and their underlying principles, production conditions, structural dynamics, prevalent destabilization mechanisms, and drug delivery applications of nanoemulsions to spike interest of those contemplating a foray in this field.

Nanoemulsions are widely used in pharmaceutical systems. Nanoemulsion formulation offers several advantages such as delivery of drugs, biological or diagnostic agents. The most important application of nanoemulsion is for masking the disagreeable taste of oily liquids. Nanoemulsion may also protect the drugs, which are susceptible to hydrolysis and oxidation. Nowadays, nanoemulsions are used for targeted drug delivery of various anticancer drugs, photo sensitizers or therapeutic agents. Nanoemulsion can also provide prolonged action of the medicaments. Overall all nanoemulsion formulation may be considered as effective, safe and with increased bioavailability. It is expected that further research and development will be carried out in the future regarding nanoemulsion.

Arguments made in this review suggest increasing influence of nanoemulsions in each and every aspect of drug delivery. Nanoemulsions are:

1) Inherently resistant to normal destabilizing mechanisms persistent in emulsions;
2) They are usually transparent which gives the cosmetic appeal, and
3) Present many opportunities of increasing oral availability of strongly lipophilic drugs.

Oral delivery was the principal concept which led to development of emulsions, and it is in this aspect that nanoemulsions are especially suited. Other routes of drug delivery are equally approachable via nanoemulsions. Their minute dimensions make them special candidates for innocuous intravenous entry. Nanoemulsions are expected to progressively become center of research and development. Nevertheless many challenges still need to be overcome, in order to ensure that nanoemulsions enter

mainstream pharmaceutical market and reach from a laboratory bench side to an actual patient bed side. Principal amongst them are the cost implications for scaling up nanoemulsion production, quest for nontoxic solvents in formulation, and also enhancing toxicity database available for various excipients employed in fabrication of nanoemulsions.

Conflicts of interest: Nil

Source of funding: None

References

Ahuja A, Ali J, Baboota S, Faisal MS, Shakeell F, Shafiq S. 2008. Stability evaluation of Celecoxib nanoemulsion containing Tween 80. Thai Journal of Pharmaceutical Sciences, 32:4–9.

Anton N, Saulnier P. 2008. Design and production of nanoparticles formulated from nano-emulsion templates-a review. Journal of Controlled Release, 128:185-199.

Asthana S, Jaiswal AK, Gupta PK, Pawar VK, Dube A, MK Chourasia. 2013. Immuno adjuvant chemotherapy of visceral leishmaniasis in hamsters using amphotericin B-encapsulated nanoemulsion template-based chitosan nanocapsules. Antimicrobial Agents and Chemotherapy, 57:1714–1722.

Aubrun OS, Simonnet JT, Alloret FL. 2004. Nanoemulsions: a new for skincare products. Journal of Colloid and Interface Science, 108-109:145-149.

Bawa R, Audette GF, Reese B. 2016. Handbook of Clinical Nanomedicine: Law, Business, Regulation, Safety, and Risk, CRC Press,

Buscall R, Davis SS, Potts DC. 1979. The effect of long-chain alkanes on the stability of oil-in-water emulsions, the significance of ostwald ripening. Colloid and Polymer Science, 257:636–644.

Capek I. 2004. Degradation of kinetically-stable o/w emulsions. Advances in Colloid and Interface Science, 107:125–155.

Charles L, Anthony A. 2011. Current state of Nanoemulsion: A review. Avaliable from:http://www.scirp.org/2011.

D'Souza S. 2014. A Review of In Vitro Drug Release Test Methods for Nano-Sized Dosage Forms. Advanced Pharmaceutical Bulletin, 1-12.

Debnath S, Satyanaryana G, Kumar V. 2011. Nanoemulsion- A Method to improve the Solubility of lipophilic drugs: A Review. Avaliable from: http ://www.pharmanest.net/2011/vol-2.

Devarajan V, Ravichandran V, 2011. Nanoemulsions: As Modified Drug Delivery Tool. International Journal of Comprehensive Pharmacy, 4(01):1-6.

Ganta S, Amiji M. 2009. Coadministration of paclitaxel and curcumin in nanoemulsion formulations to overcome multidrug resistance in tumor cells. Molecular Pharmaceutics, 6:928–939.

Ganta S, Sharma P, Paxton JW, Baguley BC, Garg S. 2010. Pharmacokinetics and pharmacodynamics of chlorambucil delivered in long-circulating nanoemulsion. Journal of Drug Targeting, 18:125–133.

Gasco MR, Gallarate M, Pattarino F. 1991. In vitro permeation of azelaic acid from viscosized microemulsions. International Journal of Pharmaceutics, 69:193–196.

Guglielmini G. 2008. Nanostructured novel carriers for topical application. Clinics in Dermatology, 26:326-331.

Hadgraft J. 2001. Skin, the final frontier. International Journal of Pharmaceutics, 224:1–18.

Hak S, Helgesen E, Hektoen HH, Huuse EM, Jarzyna PA, Mulder WJ, Haraldseth O, Davies L, Cde. 2012. The effect of nanoparticle polyethylene glycol surfacedensity on ligand-directed tumor targeting studied in vivo by dualmodality imaging. ACS Nano 6: 5648–5658.

Haskell R. 2012. Physical Characterization of Nanoparticles. Nanopart tech drug delivery. 159:126-132.

Higuchi WI, Misra J. 1962. Physical degradation of emulsions via the molecular diffusion route and the possible prevention. Journal of Pharmaceutical Sciences, 51:459-466.

Huang H, Yu Q. 2012. Improving the oral bioavailability of curcumin using novel organogel-based nanoemulsions. Journal of Agricultural and Food Chemistry, 60:5373–5379.

Kahlweit M. 1975. Ostwald ripening of precipitates. Advances in Colloid and Interface Science, 5:1–35.

Kansal S, Tandon R, Dwivedi P, Misra P, Verma PR, Dube A, Mishra PR. 2012. Development of nanocapsules bearing doxorubicin for macrophage targeting throughthe phosphatidylserine ligand: a system for intervention in visceral leishmaniasis. Journal of Antimicrobial Chemotherapy, 67:2650–2660.

Kazimiera A, Katarzyna Z, Agnieszka H, Adam J. 2009. Biocompatible nanoemulsions of dicephalic aldonamide-type surfactants: Formulation, structure and temperature influence. Journal of Colloid and Interface Science, 334:87–95.

Kemken J, Ziegler A, Muller BW. 1992. Influence of supersaturation on the pharmacodynamic effect of bupranolol after dermal administration using microemulsions as vehicle. Pharmaceutical Research, 9:554-558.

Ker GS, Lieberman HA, Rieger MM. 2002. Pharmaceutical dosage forms. Disperse System Marcel Dekker, 2(3):339–340.

Kh. Hussan R. 2011. Nanoemulsion as a Novel Transdermal Drug Delivery System. International Journal of Pharmaceutical Sciences and Research, 2(8):1938-1946.

Kim YH, Ghanem AH, Mahmoud H, Higuchi WI. 1992. Short chain alkanols as transport enhancers for lipophilic and polar/ionic permeants in hairless mouse skin: mechanism(s) of action. International Journal of Pharmaceutics, 80:17-31.

Kreilgaard M, Kemme MJB, Burggraaf J, Schoemaker RC, Cohen AF. 2001. Influence of a microemulsion vehicle on cutaneous bioequivalence of a lipophilic model drug assessed by microdialysis and pharmacodynamics. Pharmaceutical Research, 18:593Y599.

Kriwet K, Müller-Goymann C. 1995. Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum. International Journal of Pharmaceutics, 125:231–242.

Kumar HR, Patra K, Pareta S. 2011. Nanoemulsion as Potential Vehicle for transdermal delivery of pure phytopharmaceuticals and poorly soluble drug. A Review: available from http://www.arjouranls.org/index.php /ijdd/index/2011.

Leong TSH, Kentish SE, Wooster TJ. 2009.Minimizing oil droplet size using ultrasonic emulsification. Ultrasonics Sonochemistry, 16:721-727.

Ma Y, Liu D, Wang D, Wang Y, Fu Q, Fallon JK, Yang X, He Z, Liu F. 2014. Combinational delivery of hydrophobic and hydrophilic anticancer drugs in single nanoemulsions to treat MDR in cancer. Molecular Pharmaceutics, 11:2623-2630.

Meng LX, Xia Y, Yang J, Ye W, Dong P, Ma Y, Jin Y, Liu. 2016. Co-encapsulation of paclitaxel and baicalein in nanoemulsions to overcome multidrug resistance via oxidative stress augmentation and P-glycoprotein inhibition. International Journal of Pharmaceutics, 513:8-16.

Monteagudo E, Gándola Y, González L, Bregni C, Carlucci AM. 2012. Development, characterization, and in vitro evaluation of tamoxifen microemulsions. Journal of Drug Delivery, 236713.

Monteagudo EY, Gándola L, González C, Bregni AM. 2012. Carlucci, Development, Characterization, and In Vitro Evaluation of Tamoxifen Microemulsions, Journal of Drug Delivery, 236713.

Mura S J. Nicolas P. 2013. Couvreur, Stimuli-responsive nanocarriers for drug delivery. Nature Materials, 12:991-1003

Napper DH. Polymeric Stabilisation of Colloidal Dispersions. Acad Press London. 1983.

Nicolosi JR, Kuo F, Kotyla T. 2008. Nanoemulsion of an anti-oxidant synergy formulation containing gamma tocopherol have enhanced bioavailability and anti-inflammatory properties. International Journal of Pharmaceutics, 363:206-213

Paolino D, Webster J. 2006. Encyclopedia of Medical Devices and Instrumentation. Drug delivery, 437-487.

Pawar VK, Panchal SB, Singh Y, Meher JG, Sharma K, Singh P, Bora HK, Singh A, Datta D, Chourasia MK. 2014. Immunotherapeutic vitamin E nanoemulsion synergies the antiproliferative activity of paclitaxel in breast cancer cells via modulating Th1 and Th2 immune response. Journal of Controlled Release, 196:295–306.

Perdiguer AC, Dachs FJG, Carreras N, Valdivia. 1997. Nanoemulsion of the oil water type, useful as an ophthalmic vehicle and process for the preparation thereof Assignee: Laboratorios Cusi, S.A. (Barcelona, ES).

Pershing LK, Parry GE, Lambert LD. 1993. Disparity of in vitro and in vivo oleic acid-enhanced b-estradiol percutaneous absorption across human skin. Pharmaceutical Research, 10:1745-1750.

Ramreddy S, Kandadi P, Veerabrahma K. 2012. Formulation and pharmacokinetics of diclofenac lipid nanoemulsions for parenteral application. PDA Journal of Pharmaceutical Science and Technology, 66:28–37.

Rapoport NY, Kennedy AM, Shea JE, Scaife CL, Nam KH. 2009. Controlled and targeted tumor chemotherapy by ultrasound-activated nanoemulsions/microbubbles, Journal of controlled Release, 138:268-276.

Shah P, Bhalodia D. 2010. Nanoemulsion: A Pharmaceutical Review. Sys Rev Pharm. 1(1):24-32.

Singh Y, S Tomar, S Khan, JG Meher, VK Pawar, K Raval, K Sharma, PK Singh, M Chaurasia, B Surendar Reddy MK. 2015. Chourasia, Bridging small interfering RNA with giant therapeutic outcomes using nanometric liposomes. Journal of controlled Release, 220:368-387.

Sinha MKB, Ganesh N. 2015. Preparation and characterization of nanoemulsion based on papaya seed

oil. Vivo Scientia, 4:72-76.

Smith S, Davis S. 1973. Proceedings: the role of molecular diffusion in the bulk stability of o-w hydrocarbon emulsions. Journal of Pharmacy and Pharmacology, 25:117.

Tadros TF. 1982. The Effect of Polymer on Dispersion Properties. Polym Adso Colloid Stab.

Tadros TF. 2004. Formation and stability of nanoemulsions. Advances in Colloid and Interface Science, 108:303-318.

Tanojo H, Junginger HE, Boddé HE. 1997. *In-vivo* human skin permeability enhancement by oleic acid: transepidermal water loss and Fourier-transform infrared spectroscopy studies. Journal of Controlled Release, 47:31-39.

Tiwari SB, MM Amiji. 2006. Improved oral delivery of paclitaxel following administrationin nanoemulsion formulations. Journal of Nanoscience and Nanotechnology, 6:3215–3221.

Trotta M. 1999. Influence of phase transformation on indomethacin release from microemulsions. Journal of Controlled Release, 60:399–405.

Zhou H, Yue Y, Liu G, Li Y, Zhang J, Gong Q, Yan Z, Duan M. 2009. Preparation and characterization of a lecithin nanoemulsion as a topical delivery system. Nanoscale Research Letters, 5:224–230.

Zhou QL, Chen ZY, Wang YX, Yang F, Lin Y, Liao YY. 2014. Ultrasound-mediated local drug and gene delivery using nanocarriers, BioMed research international, 963-891.