**Chapter 45**

**Nano-emulsions as Potential Drug Discovery and Delivery Systems for Bioactive Compounds: Preparation, Characterization, and Applications in Drug/Pharmaceutical Industry**

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**45.1. Introduction**

The goal of an optimum drug delivery system is to maximise therapeutic benefit while reducing toxicity. Dosage forms have evolved over time and with advances in science and technology, from basic mixes and pills to extremely sophisticated systems known as innovative drug delivery systems. Nanoemulsions are innovative drug delivery devices made up of emulsified oil and water droplets with diameters ranging from 50 to 1000 nanometers. The average droplet size is usually between 100 and 500 nm, and it can be oil-in-water (o/w) or water-in-oil (w/o), depending on whether the particle's centre is oil or water. Pharmaceutical surfactants are used to make nanoemulsions, which are generally considered harmless (GRAS). In the aqueous phase, the surfactant type and concentration are chosen to offer good stability against coales cence. Nanoemulsions are made from a variety of oils, including natural, semi-synthetic, and synthetic oils. Nanoemulsions are suitable drug delivery vectors because of their ability to dissolve large amounts of low solubility medicines, as well as their mutual compatibility and ability to shield the medications from hydrolysis and enzymatic destruction (Ravi and Padma, 2011). Improved drug loading, reduced patient variability, advanced drug solubility and bioavailability, protection from enzymatic degradation, and controlled drug release are some of the key benefits of nanoemulsions as medicine transport vehicle (Kotta et al., 2012).

There are a variety of approaches for improving the absorption of poorly water-soluble medicines, including the use of lipid-based systems. Thus, improving water solubility is a worthwhile goal in order to construct them into accessible dose forms. For efficient delivery of weakly water-soluble pharmaceuticals, a variety of novel techniques are being developed, includes the creation of flexible solid forms formulation, microemulsions, melt extrusion, nanoparticles, salt creation, solid dispersions, with water-soluble complexes are created. The lipid-based formulation technique is the most widely accepted strategy (Dixit and Nagarsenker, 2008; Shafiq et al., 2007). Lipid-based formulations improve absorption by increasing solubility, extending gastric residence time, boosting the intestinal lymphatic transport channel, changing intestinal permeability, lowering efflux transporter activity, and slowing metabolism. Self-emulsifying systems, suspensions, nanoemulsions, and solutions are all available as options in lipid-based formulations.

High- and low-energy technologies can be used to make nanoemulsions. Stable nanoemulsions can be made using both high-energy and low-energy approaches. A high-pressure mixer or an ultrasound device can be used to prepare nanoemulsions utilising the high-energy emulsification method. Low-energy method for making nanoemulsions includes phase inversion and self-emulsification procedures. Low-energy emulsification methods rely on the constituents' phase behaviour and characteristics, and they use the system's stored energy to produce micro droplets. Emulsification can be induced by altering system factors such as temperature and composition, which impact the system's hydrophilic lipophilic equilibrium.

This study concentrated on current breakthroughs within nanoemulsion preparation, characterization with drug delivery applications. Nanoemulsions can be made to deliver medications via a variety of methods. When administering to transport orally active drugs, nanoemulsion are well-tolerated both orally and on the mucous membranes and skin. As a result, they're employed to transport medications that treat oral herpes, vaginitis, bacterial and fungal infections, and other conditions. Nanoemulsions particles may bind to the lipid-containing organisms' membranes, allowing for easier penetration and transmission. In comparison to other emulsion systems, nanoemulsions require less surfactant. Because tiny particles easily pass the absorption membrane, this can boost the bioavailability of poorly soluble medicines. Furthermore, the tiny size provides a wide surface area, facilitating solubilization and penetration through the epithelium layer or skin (Sutradhar and Amin, 2013).

**45.2. Nanoemulsion formulation**

***45.2.1. Nanoemulsions are made from several materials***

Oils, surfactants and co-surfactants, as well as an aqueous phase, are used to make nanoemulsions (Adnan et al., 2009). Captex 8000, Captex 355, Myritol 318, Isopropyl myristate, Capryol 90, Witepsol, triacetin, Sefsol-218, isopropyl myristate, olive oil, castor oil, and other oils are utilised in the creation of nanoemulsions. The drug's solubility within oil droplets is a significant criterion in oil selection. That’s also particularly important in the context of oral method development, since the capability of a nanoemulsions can keep a medicine in a soluble form state can heavily affected by drug's soluble in the oil droplets. While hydrophilic medications are better soluble in water-in-oil nanoemulsions, highly bioavailable medicines are better soluble in “oil-in-water” nanoemulsion. In the development of nanoemulsions for poorly soluble pharmaceuticals, drug loading in the formulation is a significant design factor that is dependent on drug solubility in various formulation components. To design steady as well as suitable limited nanoemulsions processes for drug carriers, an understanding of factors influencing drug loading capacity while maintaining the system's ability to undergo monophasic dilution with water and minimising the tendency for drug precipitation or crystallisation in diluted systems is essential (Lawrence and Rees, 2000; Narang et al., 2007). Due to their inability to dissolve substantial doses of lipophilic medicines, edible oils are rarely used. Furthermore, making a nanoemulsion with poor drug solubility oil would necessitate using more oils to integrate the targeted medicine dose, would necessitate using a greater surfactants concentrations for accomplish oils emulsification, thus emhancing this system's toxicities. Novel semi-synthetic medium chain derivatives with surfactant characteristics are gradually and successfully replacing traditional medium chain triglyceride oils (Constrantinides, 1995; Karim et al., 1994).

Nonionic, zwitterionic, cationic, and anionic surfactants are all employed to stabilise nanoemulsions. Cremophor RH 40, Capryol 90, Gelucire 44/14, 50/13, Imwitor 191, 742, 780 k, 928, 988, Lauroglycol 90, Plurol Oleique CC 497, Softigen 701, 767, Labrafil CS, M, 2125 CS, Poloxamer 124 and 188, PEG MW > 4000, Cremophor EL, Tween, Labrasol Toxicity problems have been linked to components of nanoemulsion-based systems. When taken orally or topically, large doses of surfactants can cause gastrointestinal and skin irritation. As a result, proper surfactant selection is critical. The rational use of the surfactant's minimal concentration in the formulation is recommended. Nonionic surfactants are less hazardous than ionic surfactants, and their critical micelle concentrations are often lower (CMCs). In addition, nonionic surfactant-based o/w nanoemulsion dosage formulations for oral or parenteral usage are predicted to give in vivo stability (Kawakami et al., 2002). As a result, selecting the right surfactants is critical. The selection of a surfactant with the right hydrophile-lipophilebalance (HLB) value is another key factor. Water-soluble detergents and co-detergents also thought may promote at interfaces and so reduce its amount of power required for create nanoemulsion, enhancing stability. For example, to generate an o/w nanoemulsion, the HLB value must be more than 10 (Kommuru et al., 2001). When diluted with water, the correct combination of low and high HLB surfactants forms a stable nanoemulsion. The type and nature of the surfactant is also important to consider; nonionic surfactants are typically chosen because they are less affected by pH and changes in ionic strength, are generally considered safe, and are biocompatible; ionic surfactants are used less frequently due to toxicological concerns. The oil's solubilization with the surfactant is also significant. It is not required that the same surfactant with good drug solubilizing ability also has good affinity for the oil phase. Surfactant–oil miscibility can thus provide an early indicator of the system's ability to generate nanoemulsions.

To create nanoemulsion systems at low surfactant concentrations, cosurfactants are used (Kreilgaard et al., 2000). Cosurfactants such as short- to medium-chain-length alcohols (C3–C8) are often used as cosurfactants to reduce interfacial tension and promote interface fluidity (Trenjarla, 1999; Attwood, 1994). They also improve the mobility of the hydrocarbon tail, allowing more oil to penetrate this region. Due to its partitioning between these phases, alcohols may also increase the miscibility of the aqueous and oily phases. Transcutol P, glycerin, ethyleneglycol, ethanol, propanol, ethanol, isopropyl alcohol, n-butanol, PEG 400, Carbitol, and propylene glycol are some of the co-surfactants utilised in nanoemulsions. The area of a nanoemulsion is frequently used as a criterion for evaluating cosurfactants. The system's nanoemulsification efficiency increases as the size of the nanoemulsion field grows. Furthermore, the most significant criterion for selecting all nanoemulsion components is that all excipients must be pharmaceutically acceptable for oral administration, topical application, and other uses, as needed, and must come under the GRAS category.

***45.2.2. Methods of preparation of nanoemulsions***

Because nanoemulsions are non-equilibrated systems (Ravi and Padma, 2011; Anton and Vandamme, 2009; Mason et al., 2006), their preparation necessitates the addition of a significant amount of either energy or surfactants, or a combination of the two. As a result, they can be formulated using either high or low energy approaches (Anton and Vandamme, 2009). Although high energy emulsification is usually employed to prepare nanoemulsion formulations, low emulsion emulsification is gaining popularity due to its extensive use and benefits in terms of formulation and stability. Because the process can be non-spontaneous, energy is frequently required in emulsion formulation. The energy required to make nanoemulsions is more than that necessary to make macroemulsions. Surfactants aid in the reduction of surface tensions between oil and water. Non-ionic surfactants, for example, have a lower surface tension than polymeric surfactants like polyethylene glycol (vinyl alcohol). The influence of the surfactant on the interfacial dilatational modulus is another significant function of the surfactant (Tadros et al., 2004). During emulsification, the interfacial area expands, resulting in a decrease in surface excess. Adsorption of surfactant from the bulk restores equilibrium, but this takes time (shorter times occur at higher surfactant activity). Dilatational modulus will not be the same for expansion and compression of the interface due to the lack or slowness of equilibrium with polymeric surfactants (Tadros et al., 2004). Surfactant mixes are commonly utilised in practise, and they have significant impacts on surface tension and dilatational modulus. Surface tension levels are lower in some surfactant combinations than in either of the two independent components. Surface action in polymer-surfactant combinations may be synergistic. During emulsification, the emulsifier plays a crucial function in preventing shear-induced coalescence. The continuous phase must have a large amount of surfactant in it. This excess allows for the quick coating of additional surface area on nano-scale droplets during emulsification, preventing shear-induced coales cence. In the continuous phase, this surplus is usually in the form of surfactant micelles. These micelles break down into monomers, which adhere quickly to the surfaces of newly formed droplets (Mason et al., 2006) (Figure 1).

**45.2.2.1. Low-energy techniques**

Low-energy emulsification technologies, as the name implies, need less energy to create nanoemulsions. To produce nano-sized emulsion droplets, these approaches rely primarily on regulation of interfacial phenomena/phase transitions and inherent physicochemical features of surfactants, coemulsifiers/co-surfactants, and oil. The condensation approach, or lower energy method, is based on phase transitions that occur during the emulsification process (Lamaallam et al., 2005; Solans et al., 2002). These phase transitions are caused by changes in the surfactant's spontaneous curvature, and they can be achieved in two ways: I at constant composition by changing the spontaneous curvature of non-ionic surfactants with temperature (the well-known Phase Inversion Temperature, PIT, widely used in industry (Izquierdo et al., 2005; Shinoda and Saito, 1968), or (ii) at constant temperature by varying the system's composition (the Emulsion Inversion Point, EIP) method (Forgiarini et al., 2001; Pey et al., 2006; Porras et al., 2008). To put it another way, a low-energy emulsification approach was devised to encourage the production of ultrasmall droplets based on the phase behaviour and attributes of the ingredients (Sonneville-Aubrun et al., 2004; Solans et al., 2005). Self-emulsification, phase transition, and phase inversion temperature approaches are examples of low-energy processes (Wang et al., 2007). The low-energy approach is intriguing since it makes use of the system's stored energy to generate microscopic droplets. This emulsification can be achieved by altering the parameters that affect the system's hydrophilic lipophilic balance (HLB), such as temperature, composition, and so on (Sole et al., 2006; Sole et al., 2010). Complexity, the need for a precise technique, and the usage of synthetic surfactants are all drawbacks. In a nutshell, the following are the most prevalent low-energy emulsification methods (Figure 1):

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**Figure 1. Preparation methos of Nanoemulsions**

*45.2.2.1.1. Phase Inversion Temperature (PIT) method*

This approach uses non-ionic surfactants' temperature-dependent solubility, such as polyethoxylated surfactants, to change their affinities for water and oil as a function of temperature. The dehydration of polyoxyethylene groups in polyethoxylated surfactants causes them to become lipophilic when heated. The PIT method of nanoemulsion production is based on these phenomena. Oil, water, and nonionic surfactants are combined at room temperature in the PIT method. The surfactant monolayer has a positive curvature, and the mixture often contains o/w microemulsions coexisting with excess oil. The polyethoxylated surfactant in this macroemulsion becomes lipophilic when it is heated, and at higher temperatures, the surfactant becomes totally solubilized in the oily phase, causing the initial o/w emulsion to phase invert to a w/o emulsion. At this point, the surfactant monolayer exhibits a negative curvature (Izquierdo et al., 2005). The non-ionic surfactant has identical affinity for the aqueous and oily phases at an intermediate temperature (also known as HLB temperature), and this ternary system has exceptionally low interfacial tension (in the order of 10-2–10-5 mNm-1) and spontaneous curvature typically reaches zero (Sole et al., 2006; Sole et al., 2010). A D-phase bicontinuous microemulsion or a mixture of a D-phase bicontinuous microemulsion and lamellar liquid crystalline phases makes up the ternary system at this stage. Rapid cooling of single-phase or multiphase bicontinuous microemulsions sustained at either PIT or a temperature above PIT (transitional-phase inversion) has been found to produce nanoemulsions with very small droplet size and polydispersity index (Shinoda and Saito, 1968). Nanoemulsions can also be made by rapidly diluting single bicontinuous microemulsions with the aqueous or oil phase (catastrophic phase inversion) to yield o/w or w/o nanoemulsions. The structure of the surfactant at HLB temperature (bicontinuous or lamellar) as well as the surfactant/oil ratio have been found to have a significant impact on the nanoemulsion's properties. Initially, it was thought that the PIT approach could be used to make o/w nanoemulsions. However, in recent years, the PIT approach has been successfully used to the fabrication of w/o emulsions and nanoemulsions. It's worth noting that obtaining w/o nanoemulsions necessitates the use of lipophilic polyethoxylated surfactants and necessary modifications to the standard PIT technique (Wang et al., 2007).

*45.2.2.1.2. Method of solvent displacement*

The solvent displacement approach for spontaneous nanoemulsion production was adapted from the polymeric nanoparticle nano-precipitation method. Oily phase is dissolved in water-miscible organic solvents like acetone, ethanol, and ethyl methyl ketone in this process. By rapidly diffusing organic solvent, the organic phase is poured into an aqueous phase containing surfactant to produce spontaneous nanoemulsion. A suitable method, such as vacuum evaporation, is used to remove the organic solvent from the nanoemulsion.

*45.2.2.1.3. Composition Method for Phase Inversion (Self-nanoemulsification Method)*

Without the need of an organic solvent or heat, this approach produces nanoemulsions at ambient temperature. The sequential addition of water into a solution of surfactant in oil, with moderate stirring and at constant temperature, produced kinetically stable nanoemulsions with small droplet size (50 nm), according to Forgirani et al., (2001). Despite the fact that the components utilised in the aforementioned study were not pharmaceutical-grade, the study opened the door to designing pharmaceutically acceptable nanoemulsions employing a similar approach. The phase transitions during the emulsification process have been linked to spontaneous nano-emulsification, which involves lamellar liquid crystalline phases or D-type bicontinuous microemulsion during the process (Forgiarini et al., 2001).

*45.2.2.1.4. Method of Spontaneous Emulsification*

Another way to make nano-sized emulsion is through spontaneous emulsification. In this approach, the chemical makeup of both the oil and aqueous phases, as well as the use of surfactants, is critical (Wang et al., 2015). This method involves three stages: (1) preparing a homogeneous lipid phase consisting of oil and a lipophilic surfactant, and another phase consisting of a water-miscible solvent and a hydrophilic surfactant; (2) forming the O/W emulsion by injecting the lipid phase into the aqueous phase under nonstop magnetic stirring; and (3) removing the aqueous phase by evaporation under reduced pressure (Izquierdo et al., 2005). Because of the high affinity of the surfactant for the oil or the aqueous phase, small droplets of dispersed phase covered with surfactant in the continuous phase will form, causing turbulence at the interface of both the dispersed and continuous phases, regardless of whether the surfactant is displaced toward the continuous phase. Turbulence at the interface of the two phases should be activated to form extremely small emulsions, and cosurfactants including ethanol, acetone, and propylene glycol can help. Oil, a surfactant, and a cosurfactant will be present in the organic phase, while water will be present in the aqueous phase. Many factors determine droplet size, including the level, type, structure, and amount of surfactant in the dispersed phase, additive or nutritive elements in the dispersed phase, level and type of the two phases and encapsulant, and the viscosity of the dispersed and continuous phases. Chemical energy released during the dilution process with a continuous phase is employed to form NEs using this approach, which is typically done at a constant temperature with no phase transitions (no change in the spontaneous surfactant curvature) in the solution during emulsification (Solans and Sole, 2012). The microemulsion will be diluted with water to create a nanoemulsion. The cosurfactant (alcohol) diffuses to the water phase from the oil/water interface, disrupting microemulsion production and making it thermodynamically unstable, resulting in the development of nanoemulsions (Taylor and Ottewill, 1994).

**45.2.2.2. High-intensity techniques**

In high energy emulsification, various mechanical methods such as high-pressure homogenization (HPH) or microfluidizers, as well as ultrasonication, have been used to create intense disruptive forces such as collision, compression, and cavitation, allowing one phase to be dispersed into another as tiny droplets (Mehrnia et al., 2015). Mechanical equipment is used to create the emulsion in high energy emulsification procedures. Despite their effectiveness in reducing particle size, these high-energy approaches are unlikely to work for thermolabile medicines and macromolecules as proteins, enzymes, retinoids, peptides, and nucleic acids (Mishra et al., 2010). This is due to the fact that high-energy technologies work at high temperatures and pressures, which can harm thermolabile or sensitive medicines as well as proteins.

*45.2.2.2.1. Homogenization at High-Pressure*

In general, high-pressure homogenizers use pressures ranging from 50 to 100 MPa. However, new technologies have lately enabled the development of an instrument that can operate at pressures up to 350 MPa (Izquierdo et al., 2005). A small gap in HPH generates a quick pressure drop across HPH of a few thousand bars; the diverse phases of oil, water, and surfactant are pushed into droplets and encounter severe shear and elongational stress, causing the droplets to be disrupted into finer droplets. The mixture is usually run through the homogenizer several times until the droplet size is consistent (Bisten and Schuchmann, 2016; Donsi et al., 2011; Gall et al., 2016). The fluid-dynamic stresses in HPH increase due to a variety of variables such as turbulence, elongational and shear stress, and cavitation. Depending on the equipment utilised, process fluid characteristics, droplet composition, and operating conditions, certain factors are superior to the others (Yong et al., 2017). Unless coalescence occurs, the droplet size will continue to decrease as the difference in pressure increases. If the pressure differential or energy densities are increased in HPH, the droplet width will shrink unless coalescence occurs. The droplet sizes, on the other hand, have an impact on the disruption unit because they influence the flow pattern, which specifies droplet breakup (Kissling et al., 2011).

Radial diffusers have an axially moveable seat that allows the flow rate to be changed by adjusting the slit width (Donsi et al., 2011). A collision area of two or more opposed emulsion jets is included in the counter-jet dispergator. Counter-jet dispergators and axial flow-nozzle systems have no moveable elements, making them appropriate for extremely high pressures. The axial flow direction of nozzle aggregates can be used to distinguish them. Simple orifices are circular holes with a diameter of 0.1–2 mm. Various disruption units produce different droplet sizes when the same energy density is utilised, according to research. The most significant benefits of HPH for industrial production are its scalability, ease of operation, efficiency, and high reproducibility (Gall et al., 2016). An emulsion is made in HPH by managing the emulsifier variation and the rate of coating the newly formed interface in the homogenizer. The formation rate of the new interface is determined by the hydrodynamic conditions within the break-up zone, the rate of energy dissipation, the viscosity of the two phases, and the residence duration in the break-up zone (Hålamsson et al., 2009). The hot and cold HPH techniques are the two approaches that can be employed in HPH. Both approaches have advantages, but the cold HPH technique is preferred for chemicals that are particularly temperature sensitive (Müller et al., 2002). The active compound is dissolved or dispersed in the melted lipid phase in both techniques; however, in the hot HPH technique, the mixture is dispersed into a hot surfactant solution above the melting point by high-speed stirring, whereas in the cold HPH technique, the mixture is cooled, ground, and then dissolved into a cold surfactant solution to form a cold pre-suspension of micronized phase (Pardeike et al., 2009). The pre-emulsion is then HPHed at high temperatures for the hot HPH technique or at room temperature for the cold HPH technique to obtain the NEs in both approaches. An extra element can be used in order to create a limited size distribution of NEs. The droplets will eventually face the peak shear rate generated by a flow-producing device during emulsification to obtain low polydispersity NEs as the number of cycles of the emulsion in HPH increases (Fryd and Mason, 2012). The main disadvantage of HPH is poor productivity and component deterioration due to excessive heat generation. Only O/W NEs with less than 20% oil phase may be successfully made using this approach, according to Sharma et al., (2013), but NEs with a high viscosity and diameters less than 200 nm cannot be prepared.

*45.2.2.2.2. Microfluidization*

The microfluidization procedure employs a device known as a'microfluidizer,' which also employs high pressure. A high-pressure positive displacement pump (500–200 psi) drives the product through the interaction chamber with small channels called microchannels within. The process then continues through the microchannels to an impingement location, where tiny submicron particles are formed. To make a coarse emulsion, the aqueous and oily phases are combined and treated in an inline homogenizer. Finally, the coarse emulsion is treated in the microfluidizer to obtain stable, small-sized NEs. The 'direct' emulsification approach does not require pre-emulsification because the dispersed phase is injected directly into the continuous phase through micro channels. This is thought to represent a significant benefit over the HPH approach (Maali and Mosavian, 2013). The microfluidizer is a high-velocity variant of a static mixer with no moving parts from a mechanical standpoint (Salvia-Trujillo et al., 2014). This approach has the advantage of being able to be used in both a laboratory and an industrial setting.

*45.2.2.2.3. Emulsification via Ultrasound*

The ultrasonic emulsification process is effective at reducing NE size. The energy to break down the particle size is provided by sonotrodes called sonicator probes, which include piezoelectric quartz crystal that may expand and contract in response to an alternating electric voltage. When the sonicator probe's tip comes into contact with the liquid, it causes mechanical vibration, which causes cavitation. The creation and collapse of vapour cavities in liquid is known as cavitation. As a result, emulsions can be made immediately with this process. It is mostly used in laboratories to make emulsion droplets as small as 0.2 m (Jaiswal et al., 2015). A two-step technique has been proposed for ultrasound emulsification: To convert the dispersed phase to a continuous phase, interfacial waves are first created in an acoustic field. The pressure variations then collapse micro-bubbles into smaller droplets as acoustic cavitation forms. The interaction between droplet break-up and droplet coalescence controls the generation of NEs droplets. Although ultrasound uses a high shear force to break droplets, the rate of droplet coalescence is also influenced by the surfactant's surface activity and concentration (Canselier et al., 2002; Gaikwad and Pandit, 2008; Kaci et al., 2017; Kobayashi et al., 2015; O’Sullivan et al., 2015). The downside of this approach is that it can only produce tiny batches of NEs. Some research has revealed that ultrasonication can produce surfactant-free, stable, and clear NEs, as described by Nakabayashi et al., (2013) employing tandem acoustic emulsification.

*45.2.2.2.4. Nanoparticles*

Making nanoparticle stabilised nanoemulsions is gaining popularity. A large number of nanoparticle formulation processes rely on NE templates, which can be made in a variety of ways. As a result, it's important to remember that the active principles and pharmaceuticals packed in nanoparticles could be impacted by these NE formation procedures (Machado et al., 2012). Drug sensitivity to temperature, high-shear devices, or even interaction with organic solvents are all possible variances. Similarly, NE formulation procedures must be chosen based on the therapeutic goals of the nano-carrier suspension and the route of administration. Making nanoparticle stabilised nanoemulsions is gaining popularity. There are a lot of nanoparticles. This necessitates more tailored nanoparticle formulation procedures (and hence NE production strategies) to the nature of the encapsulated medicines as well as the preferred delivery route (Kang et al., 2018; Sutradhar and Amin, 2013). Water drops self-disperse within the oil if it has the necessary characteristics and a high concentration of nanoparticles. The nanoparticles will then self-assemble to form nanoemulsions around them (Nakabayashi et al., 2013). Primo et al., created O/W nanoemulsions with suspended magnetic nanoparticles as the continuous phase (2007). This research combined colloidal nanoparticles with biocompatible magnetic fluids to create a new drug delivery system (DDS) for use in photodynamic therapy (PDT) and magnetic hyperthermia.

Furthermore, the various types or morphologies of the produced nanoparticles can be classified as polymeric nanospheres, solid lipid nanoparticles (SLNs), or polymeric or lipid nanocapsules (Anton et al., 2008). The connections between NE formation procedures and nanoparticle morphology are not evident or systematic, and they should be approached with caution (Mehnert and Mäder, 2012).

*45.2.2.2.5. High Shear Mixers*

In the sectors of agricultural and food processing, as well as chemical reaction processes, high shear mixers have been widely utilised in energy-intensive processes such as homogenization, dispersion, emulsification, grinding, dissolving, and cell disruption. High rotor tip speeds (ranging from 10 to 50 m/s), highly localised energy dissipation rates near the mixing head, very high shear rates (ranging from 20,000 to 100,000 s-1), and relatively higher power consumption than conventional mechanically stirred vessels characterise the mixers, which are caused by centrifugal forces generated by the relative motion. Batch and inline variants of high shear mixers are available. Inline high shear mixers feature either a blade screen or a rotor stator teethed arrangement, whereas batch units have radial or axial discharged kinds. Inline high shear mixers can be used in conjunction with batch high shear mixers in a circulation loop downstream of a tank equipped with the batch unit. This can help to increase product quality while also reducing processing time. They are made up of a fast-turning rotor and a stationary stator. The substance or emulsion will continuously attract into the mixing head as the rotor turns, and will be discharged at a high velocity via the stationary stator. As the hydraulic shear mixes the emulsion quicker, the size of the droplets decreases (Zhang et al., 2012).

**45.2.3 Advantages and Drawbacks**

The advantages of NEs are numerous. Because NEs have a higher surface area, they are appropriate for drug administration (Li and Chiang, 2012). This could boost drug absorption through a variety of pathways. A wide surface area also has an impact on the drug's transport characteristics, which is a key aspect in ensuring long-term and targeted drug delivery (Lawrence and Rees, 2000). Furthermore, because decrease under gravity pull may be prevented to a significant extent, NEs are often more stable than traditional emulsions due to their tiny size. As a result, NEs have been found to have no creaming or sedimentation, allowing for prolonged shelf storage (Bhattacharjee, 2019). There are several ways to make NEs, and some of them, with the help of a surfactant in their formulations, use very little or no energy (heat or mixing). There are, however, techniques that require mechanical instruments to shatter the droplets into smaller sizes. This demonstrates that NEs are adaptable and may be customised to meet specific needs. Aside from that, NEs have been employed to aid in the solubilization of lipophilic medicines and the masking of their bad taste. NEs are a promising strategy to distribute fish oil into liquid food systems, as they protect the oil from oxidation, boost oral bioavailability, and mask off-tastes (Kadappan et al., 2018). In mice, NEs improved vitamin D absorption, according to a study (Kadappan et al., 2018). Another study (Tiwari et al., 2006) found that NEs could improve the oral bioavailability of poorly soluble medicines. Because NEs are mostly made up of water, oil, and a surfactant, they are not considered harmful. The surfactant used in the NEs has been determined to be safe to consume. As a result, it is less prone to irritate humans. Furthermore, when compared to microemulsions, NEs require lower surfactant content. NEs are thought to be the finest alternatives for liposomes that are less stable. NEs are better at transporting lipophilic substances than liposomes because of their lipophilic core. They, like liposomes, help active substances penetrate the skin and hence boost their concentration in the skin. Many types of medications with diverse physical qualities and chemical structures can be delivered via NEs. NEs are also used in a range of fields, including food, medicine delivery, cosmetics, pharmaceuticals, and material synthesis (Ren et al., 2019; Nirmal et al., 2018).

**45.2.4. Factors affecting nanoemulsion stability during formulation**

Although nanoemulsions improve medication physical and chemical stability, drug product stability is one of the issues connected with nanoemulsion development (Shafiq et al., 2007; Shakeel et al., 2008; Shakeel et al., 2008; Baboota et al., 2007). Nanoemulsions are tested for stability by storing them in the refrigerator and at room temperature for several months. During this time of storage, the viscosity, refractive index, and droplet size are determined. Formulation stability is indicated by small variations in these characteristics. Nanoemulsions can also be subjected to accelerated stability tests. Nanoemulsion formulations are stored at elevated temperatures in this case, and samples are taken at regular intervals and evaluated for drug content using stability indicating testing methods. At each time interval, the amount of medication destroyed and remaining in the nanoemulsion formulation is determined (Mason et al., 2006). Controlling factors such as the kind and concentration of surfactant and cosurfactant, the type of oil phase, the procedures employed, process variables, and the addition of additives can improve the stability of nanoemulsion formulations development (Shafiq et al., 2007; Shakeel et al., 2008; Shakeel et al., 2008; Baboota et al., 2007; Mason et al., 2006; Haritha et al., 2013). Overall, a nanoemulsion formulation for pharmaceutical administration might be regarded effective, safe, and patient-friendly.

Among the factors to consider during the preparation of nanoemulsion are the following (Haritha et al., 2013):

1. Surfactants must be carefully chosen in nanoemulsion manufacturing because the goal is to achieve an ultra low interfacial tension at the oil-water contact.
2. The surfactant concentration must be sufficient to deliver the required number of surfactant molecules to stabilise the nano droplets.
3. To stimulate the formation of nanoemulsions, the contact must be flexible.

**45.3. Nanoemulsions: Characterization**

Compatibility of nanoemulsion components, isotropicity of the formulation, assay, uniformity of content, appearance, pH, viscosity, density, conductivity, surface tension, size and zeta potential of the dispersed phase, and other physical and chemical tests related to oral liquid dosage forms are included in the characterization of nanoemulsions (Narang et al., 2007; Gurvey and Benita, 2004; Gershanik et al., 1998; Ghosh et al., 2006; Lawrence and Rees, 2000; Chiesa et al., 2008; Craig et al., 1995; Debnath et al., 2011; Tin-hinan et al., 2011; Karthikeyan et al., 2012; Mandal and Bera, 2012). Differential scanning calorimetry (DSC) offers information on the interactions of different components, while polarisation microscopy with crossed polarizers is used to check the formulation's isotropicity (Chiesa et al., 2008). Visual assessment can be used to evaluate the self-nanoemulsification process. The rate of emulsification and droplet size distribution would be used to calculate its efficiency. Turbidity measurements are taken to determine the dispersion's rapid equilibrium and the reproducibility of the procedure. Because it impacts the rate and amount of drug release as well as absorption, the droplet size of the emulsion is a critical factor in self-nanoemulsification performance. For determining the size of nanoemulsion droplets, photon correlation spectroscopy (PCS) and light scattering techniques such as static light scattering (SLS) and dynamic light scattering (DLS) are beneficial (Craig et al., 1995). At the macroscopic level, viscosity, conductivity, and dielectric techniques provide useful information. Measurements of viscosity, for example, can reveal the presence of rod-like or worm-like reverse micelles and conductivity measurements can be used to determine if a nanoemulsion is oil-continuous or water-continuous, as well as to monitor phase inversion processes (Chiesa et al., 2008). Dielectric measurements are an effective way to investigate both the structural and dynamic properties of a nanoemulsion system. Self-diffusion nuclear magnetic resonance (SD NMR) and small angle xray scattering were used to investigate the structural properties of nanoemulsions (SAXS). Freeze fracture electron microscopy has also been used to investigate nanoemulsion structure; however, in order to maintain the structure and avoid artefacts, the sample must be rapidly cooled (Debnath et al., 2011; Tin-hinan et al., 2011; Karthikeyan et al., 2012). The polarity of nanoemulsion droplets is also an essential component in determining emulsification efficiency. The polarity of oil droplets is affected by the HLB, chain length and degree of unsaturation of fatty acids, molecular weight of the hydrophilic component, and emulsifier content. Polarity describes the medicinal compound's attraction for oil and/or water, as well as the forces that result. The polarity encourages rapid drug release into the aqueous phase. Another aspect to consider is the charge of the oil droplets in nanoemulsions. Due to the presence of free fatty acids, it is usually negative; however, incorporating a cationic lipid, such as oleylamine at a concentration of 1-3 percent, will result in cationic nanoemulsions (Mandal and Bera, 2012; Kayes, 1999).

The following subheadings could be used to quickly highlight the parameters usually utilised in nanoemulsion evaluation:

1. **Morphology:** Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to examine the morphology of nanoemulsions (SEM). The globules are imaged in three dimensions using SEM (Kayes, 1999). The samples are evaluated at various magnifications and at a sufficient acceleration voltage, usually 20 kV. SEM provides a thorough examination of the surface morphology of the dispersed phase in the formulation. To achieve an automatic analysis result of the form and surface morphology, image analysis software can be used (Barea et al., 2010). Higher resolution photos of the disperse phase can be produced using TEM. The sample is negatively stained with a 1% phosphotungstic acid aqueous solution or by dropping a 2% uranyl acetate solution onto a 200 µm mesh size PioloformTM-coated copper grid or a microscopic carbon-coated grid with a micropipette, then examined under a transmission electron microscope at the appropriate voltage. A digital image processing programme can be used to do qualitative measurements of TEM micrograph diameters and size distribution (Samah et al., 2010). To investigate the structure and behaviour of nanoemulsions, more advanced techniques such as x-ray or neutron scattering, atomic force microscopy, or cryo-electron microscopy are often required (Izquierdo et al., 2005).
2. **c) Zeta potential, droplet size, and polydispersity:** Brownian motion causes changes in the intensity of scattering by droplets/particles, which is studied using dynamic light scattering (DLS) or photon correlation spectroscopy (PCS) (Ruth et al., 1995). PCS can use a particle size analyzer to determine the size, polydispersity, and zeta potential of nanoemulsion droplets. This instrument also calculates the polydispersity index, which is a metric for the size distribution's broadness determined from a cumulative analysis of dynamic light scattering. The polydispersity index measures the dispersion's quality or homogeneity (Li et al., 2011). PCS calculates the particle diameter z-average. Another method for determining particle size is laser diffraction. This technique yields a volume-based basic particle size distribution that is stated in terms of the volume of equivalent spheres (DN percent) and the weighted mean of the volume distribution (mass mean diameter).
3. **Viscosity:** A viscometer is used to accomplish this. The surfactant, water, and oil components, as well as their concentrations, determine the viscosity of nanoemulsions. Increased water content reduces viscosity, but decreased surfactant and cosurfactant content raises interfacial tension between water and oil, resulting in increased viscosity. Viscosity is critical for medication release stability and efficacy. Because nanoemulsion carrier formulations are essentially oil-in-water, they are less greasy than water-in-oil formulations and have lower apparent viscosities. As a result, they should release active ingredients more quickly and wash off readily after being applied to the skin. The rheological properties of nanoemulsion carriers can be assessed using a variety of equipment and methodologies. Viscosity change monitoring is a technique for determining the stability of liquid and semi-solid preparations, including nanoemulsion formulations (Chiesa et al., 2008).
4. **e) Skin permeation in vitro:** In the case of transdermal formulations, the Franz diffusion cell is employed to acquire the drug release profile of the nanoemulsion formulation. Confocal scanning laser microscopy can be used to see how far the discharged substance penetrates the skin. Dispersing an amount of the preparation in the donor compartment of a Franz cell with a membrane as a barrier and monitoring the appearance of the encapsulated drug in the receptor compartment, which is usually containing phosphate buffer saline (PBS, pH 7.4) and stirring at 100 rpm at 37 ± 1°C can be used to determine in vitro drug release. At regular intervals, samples of the dispersion (1 ml) are removed from the receptor medium and replaced with an identical amount of the medium. The drug discharged is then evaluated using HPLC or UV-Vis spectroscopy at the wavelength of peak absorption of the drug (e.g., Millipore, USA) (Agrawal et al., 2010). The diffusion cell is a common and alternate method of ex-vivo release investigation. The skin of the ear or abdomen is carefully sliced away, and the underlying cartilage and lipids are meticulously removed. Skin is cut to the appropriate size and placed on the diffusion cell, which had previously been filled with receptor solution. The instrument is then initiated after samples of the vesicular preparation are put to the dorsal surface of the skin. Samples are taken from the receptor media and refilled with equal volumes of the medium at intervals of up to 24 hours, and the withdrawn samples are evaluated for drug permeation using HPLC or UV spectroscopy (Touitou et al., 2000; Bendas and Tadros, 2007). For in vitro release investigations, a semipermeable membrane such as regenerated cellulose could be utilised instead of skin (Jain et al., 2007; Dave et al., 2010).
5. **g) Pharmacodynamic/bioavailability studies in vivo:** The preparation is applied or administered to a whole live animal in an in vivo release study, also known as dermatopharmacokinetics. After that, blood samples are taken at intervals, centrifuged, and the plasma (deproteinized) is tested for drug content using HPLC. The results of in vitro and in vivo tests are extrapolated to reflect the medication formulation's bioavailability. Furthermore, depending on the pharmacological properties of the integrated drug, the pharmacodynamic features of nanoemulsion formulations are evaluated (Solans et al., 2005; Wang et al., 2007; Sole et al., 2006; Sole et al., 2010; Graves et al., 2005; Jafari et al., 2007; Quin and Mc Clement, 2011; Shafiq et al., 2007; Shakeel et al., 2008; Shakeel et al., 2008; Baboota et al., 2007; Mason et al., 2006; Haritha et al., 2013; Gursoy and Benita, 2004; Debnath et al., 2011).

**45.4. Nanoemulsions are used in medicine delivery.**

Cosmetics and transdermal drug delivery, cancer therapy, vaccine delivery, prophylactic in bio-terrorism attacks, non-toxic disinfectant cleaner, cell culture technology, formulations for improved oral delivery of poorly soluble drugs, ocular and otic drug delivery, intranasal drug delivery, parenteral drug delivery, and pulmonary drug delivery are just some of the applications for nanoemulsions (Figure 2).

***45.4.1. Cosmetics applications***

Nanoemulsions have recently gained in prominence as suitable carriers for regulated delivery of cosmetics and enhanced dispersion of active substances in specific skin layers. Nanoemulsions are better than liposomes at transporting lipophilic drugs because of their lipophilic interior. Nanoemulsions, like liposomes, help active substances penetrate the skin and hence increase their concentration in the skin. Another benefit is that the little droplet's large surface area allows for excellent distribution of the active to the skin. Nanoemulsions are gaining more and more attention as a result of their unique bioactive properties. This may reduce trans-epidermal water loss (TEWL), implying that the skin's barrier function is improved. Because nanoemulsions do not have the creaming, sedimentation, flocculation, or coalescence that microemulsions do, they are suitable in cosmetics. Using high-energy equipment during the manufacturing process helps prevent the introduction of potentially irritating surfactants. PEG-free cosmetic nanoemulsions have also been created, with compositions demonstrating good stability (Rutvij et al., 2011; Yashpal et al., 2013; Charles and Attama, 2011; Subhashis et al., 2011; Surbhi and kumkum, 2012).

***45.4.2. Nanoemulsions with antimicrobial properties***

Antimicrobial nanoemulsions are o/w droplets with diameters ranging from 200 to 600 nanometers. Surfactants and alcohol stabilise them, which are made of oil and water. The nanoemulsions are effective against bacteria such as *E. coli, Salmonella*, and *Staphylococcus aureus*; enveloped viruses such as HIV and herpes simplex; fungi such as candida and dermatophytes; and spores such as anthrax. The particles of nanoemulsions are thermodynamically forced to fuse with lipid-containing organisms. The electrostatic interaction between the cationic charge of the emulsion and the anionic charge on the pathogen aids this fusion. When enough nanoparticles bind to pathogens, a portion of the energy held within the emulsion is released. The active element, as well as the energy released, destabilises the pathogen's lipid membrane, causing cell death and lysis. Additional germination boosters are added to the emulsion in the case of spores. The germinating spores become vulnerable to the antibacterial effect of the nanoemulsions once germination begins. The very selective toxicity of nanoemulsions to bacteria at concentrations that are non-irritating to skin or mucous membranes is one of its features. The minimal amount of detergent in each droplet gives nanoemulsions their safety range, but when they function in concert, these droplets contain enough energy and surfactant to disrupt targeted microorganisms without harming healthy cells. Nanoemulsions can provide topical antibacterial activity previously only possible with systemic medicines (Rutvij et al., 2011; Yashpal et al., 2013; Charles and Attama, 2011; Subhashis et al., 2011).

***45.4.3. Prophylactic action in bioterrorism attacks***

Nanoemulsions have been studied as a prophylactic medicinal dosage form, a human protective medication, to prevent individuals from being exposed to bio-attacks such as Anthrax and Ebola, due to their antibacterial activity. The US Army (RestOps) tested the broad-spectrum nanoemulsions on surfaces for disinfection of Anthrax spore in December 1999. RestOps examined it again as a chemical decontamination agent in March 2001. This method has been used to treat gangrene and clostridium botulism spores, and it can even be used to save limbs from infected wounds. The nanoemulsions are marketed as NANOSTATTM (Nanobio Corp.) and can be formed as a cream, foam, liquid, or spray to disinfect a wide range of materials (Figure 2).

***45.4.4. Role of Nanoemulsions in vaccines delivery***

To vaccine against the human immunodeficiency virus, this medicine delivery device employs nanotechnology (HIV). HIV has recently been discovered to infect the mucosal immune system. As a result, strengthening mucosal immunity with nanoemulsions could be crucial in the future fight against HIV (Zhang et al., 2012). In contrast to typical vaccine approaches, the oil-based emulsion is administered through the nose. Recent study suggests that vaginal mucosa immunity can be achieved by injecting vaccines into the nasal mucosa (Rutvij et al., 2011; Yashpal et al., 2013; Charles and Attama, 2011; Subhashis et al., 2011). In order to elicit an immunological response, nanoemulsions are employed to transfer inactivated organisms to a mucosal surface. Clinical studies for the first vaccine applications, an influenza vaccine and an HIV vaccine, are now possible. The nanoemulsion acts as an adjuvant for proteins applied to the mucosal surface and aids antigen presentation cell absorption. The creation of particular IgG and IgA antibodies, as well as cellular immunity, result in a strong systemic and mucosal immune response. Animals can be protected against influenza following a single mucosal encounter to the virus mixed with thenanoemulsions, according to research. Animals treated to recombinant gp120 in nanoemulsions on their nasal mucosa produce strong HIV responses, indicating that this material could be used as an HIV vaccine. Additional research is being conducted to complete proof of concept animal trials for other vaccinations, such as Anthrax and Hepatitis B. NanoBio (Ghosh et al., 2013) has licenced this technology from the University of Michigan.

**Figure 2. Applications of Nano-Emulsion in Drug Delivery Systems**

***45.4.5. Non-toxic disinfecting cleaners using nanoemulsions***

Nanemulsions have been used to clean disinfectants. EnviroSystems has developed a nontoxic disinfection cleaner for use in everyday sectors such as healthcare, travel, food processing, and military applications. They have been reported to kill tuberculosis and a wide range of viruses, bacteria, and fungus in 5 to 10 minutes without the risks associated with other disinfectants. There are no warning labels required for this product. It is non-irritating to the eyes and can be absorbed through the skin, breathed, or eaten safely. The disinfection formulation is made up of nanospheres of oil droplets smaller than 100 m in diameter that are suspended in water to generate nanoemulsions that only require a little amount of the active component, parachlorometaxylenol. Surface charges on the nanospheres efficiently penetrate the surface charges on microbe membranes, much like an electric fence. The formulation allows parachlorometaxylenol to target and penetrate cell walls rather than 'drowning' cells. As a result, parachlorometaxylenol can be used at concentrations that are I-2 times lower than conventional disinfectants, with no harmful effects on humans, animals, or the environment (Rutvij et al., 2011; Yashpal et al., 2013; Charles and Attama, 2011; Subhashis et al., 2011).

Other microbial disinfectants require large quantities of their active chemicals to surround the pathogen cell wall, causing the microbe to disintegrate and, in theory, drown in the disinfection solution. The disinfectant is non-flammable, making it safe to store and use in potentially hazardous situations. It has no oxidising, acidic, or ionic properties. It won't corrode plastic, metals, or acrylic, making it perfect for use on instruments and equipment. Because it is ecologically friendly, it eliminates the financial and health hazards associated with hazardous chemical disposal. The disinfection cleaner is a broad-spectrum disinfectant that can be used on any hard surface, such as equipment, walls, fixtures, counters, and floors. One product can now replace many others, reducing inventory and freeing up important storage space. Chemical disposal expenditures can be eliminated, as well as disinfection and cleaning costs. EcoTru TM (EnviroSystems) was the brand name (Rutvij et al., 2011; Yashpal et al., 2013; Charles and Attama, 2011; Subhashis et al., 2011).

***45.4.6. Application of Nanoemulsions in cell culture technology***

In vitro experiments and the production of biological substances such as antibodies and recombinant proteins are both done with cell cultures. The culture media can be supplemented with a wide number of chemicals or blood serum to optimise cell development. It was extremely difficult to make oil-soluble chemicals available to the cells in the media, and only a small amount of lipophilic compounds could be absorbed by the cells. Nanoemulsions are a novel delivery system for oil-soluble compounds to human cell cultures. The technology is built around phospholipid-stabilized nanoemulsions. This nanoemulsion is transparent and can be sterilised by passing it through 0.1 mm filters. Oil droplets in nanoemulsions are easily absorbed by cells. As a result, the encapsulated oil-soluble compounds have a high bioavailability in cultured cells.

The following are some of the advantages of employing nanoemulsions in cell culture technology:

* Improved cellular uptake of oil-soluble nutrients.
* Increase the viability and proliferation of cultured cells.
* Allows oil-soluble drug toxicity studies in cell cultures (Venkatesan et al., 2005; Venkatesan, 2006; Verreck and Brewster, 2004; Breitenbach, 2002).

***45.4.7. Improved oral administration of poorly soluble medicines using nanoemulsion formulations***

The formulation of nanoemulsions was created to improve the oral bioavailability of hydrophobic medicines. As a model hydrophobic medication, paclitaxel was used. Pine nut oil was used as the internal oil phase, water as the external phase, and egg lecithin as the principal emulsifier in the o/w nanoemulsions. To provide the emulsions positive and negative charge, stearylamine and deoxycholic acid were utilised. The nanoemulsions were produced with particle sizes ranging from 100 to 120 nm and zeta potentials ranging from 34 to 245 mV. In comparison to the control water solution, oral administration of nanoemulsions resulted in a considerably greater concentration of paclitaxel in the systemic circulation. The findings of this study imply that Nanoemulsions are a promising new formulation for increasing hydrophobic medication oral bioavailability (Rutvij et al., 2011; Yashpal et al., 2013; Charles and Attama, 2011; Subhashis et al., 2011).

***45.4.8. Ocular and otic medication delivery using nanoemulsions***

One of the most fascinating and complex initiatives facing pharmaceutical scientists is ophthalmic medication delivery (Hughes and Mitra, 1993). Because of lacrimal secretion and nasolacrimal drainage in the eye, it is well knowledge that using eye drops as a traditional ocular delivery strategy results in poor bioavailability and therapeutic response (Patton and Robinson, 1976; Sieg and Robinson, 1977). In a few minutes, the majority of the medication is emptied from the precorneal area. As a result, to achieve the intended therapeutic effects, regular instillation of concentrated solutions is required (Chein et al., 1982). However, the main part of the supplied medicine is carried to the gastro intestinal system via the nasolacrimal duct, where it may be absorbed and cause side effects (Middleton et al., 1990). To maximise the drug's effectiveness, a dose form that increases the drug's contact time in the eye should be chosen. This may enhance patient compliance by increasing bioavailability, reducing systemic absorption, and reducing the need for frequent dosing. Some of these issues could be solved with nanoemulsions. Due to their multiple advantages, such as sustained action and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humour, dilutable nanoemulsions are strong drug delivery vehicles for ophthalmic usage. The antiglaucoma medication dorzolamide hydrochloride was developed into an eye nanoemulsion with high therapeutic efficacy and a long-lasting impact by Ammar et al., (2009). The physicochemical features of these nanoemulsions were satisfactory, and the drug release was delayed. For those preparations with outstanding qualities, a Draize rabbit ocular irritation test and histological investigation demonstrated that they were nonirritant. In comparison to either the drug solution or the market product, a biological evaluation of dorzolamide hydrochloride nanoemulsions on normotensive albino rabbits revealed that these products had higher therapeutic efficacy, faster onset of action, and a longer impact. In comparison to conventional eye drops, the study found that dorzolamide hydrochloride in a nanoemulsion form provided a more intensive treatment of glaucoma, a lower number of treatments per day, and improved patient compliance.

**45.4.9. Nanoemulsions as a transdermal delivery vehicle**

Due to the convenience of drug delivery through the skin to the systemic circulation for a variety of clinical problems, there has been a lot of interest in this area (Muller-Goymann, 2004; Gaur et al., 2009). It has the advantage of steady-state regulated drug delivery over a long period of time, as well as self-administration, which is not always possible with the parenteral route. The patient can remove the transdermal patch at any time to reduce the drug input. Nanoemulsions have a nice skin sensation due to their transparency and fluidity. A further benefit is the complete absence of gastrointestinal adverse effects such as inflammation and bowel ulcers, which are almost always linked with oral delivery. Cardiovascular ailments, Parkinson's and Alzheimer's illnesses, anxiety, depression, and other diseases and disorders have all been treated with transdermal medicinal treatments. However, the barrier imposed by the skin for good bioactive penetration is a major drawback that limits the utilisation of this form of administration. The three main avenues for medications to penetrate the skin are through the hair follicles, sweat ducts, or straight through the stratum corneum, which severely limits their absorption and bioavailability. The principal skin barriers must be addressed in order to optimise medication pharmacokinetics and targeting. Controlling drug redistribution across the cutaneous blood and lymph vascular system is also necessary. Nano-sized emulsions can easily permeate skin pores and enter the systemic circulation, where they are channelized for efficient delivery (Ravi and Padma, 2011). Caffeine has been used to treat various forms of cancer through oral administration. For transdermal medication delivery, water-in-oil nanoemulsion formulations of caffeine have been produced. When these medications were compared to aqueous caffeine solutions in vitro, the nanoemulsion loaded pharmaceuticals showed a considerable increase in permeability metrics (Shakee and Ramadan, 2010). The use of nanoemulsions in transdermal drug delivery is an important field of drug delivery research since it improves therapeutic efficacy as well as medication bioavailability without causing any side effects. It's also seen to be a promising approach because of its excellent storage stability, low preparation cost, thermodynamic stability, lack of organic solvents, and strong production feasibility. They've also made medication bioavailability and plasma concentration profiles repeatable. These systems are currently being employed to deliver dermal and surface effects, as well as to penetrate deeper into the skin (Ravi and Padma, 2011). In vitro (Kreilgaard et al., 2000; Osborne et al., 1991; Trotta et al., 1996; Delgado-Charro et al., 1997; Dreher et al., 1997; Schmalfus et al., 1997; Alvarez-Figueroa and Blanco-Mendez, 2001; Rhee et al., 2001; Lee et al., 2003), as well as in vivo (Kemken et al., 1992; Kreilgaard, 2001; Kreilgaard et al., 2001), many studies have shown that nanoemulsion formulations have superior trans-dermal and dermal transport capabilities. Many medications exhibit better transdermal absorption in nanoemulsions than in traditional topical formulations like emulsions and gels (Ktistis and Niopas, 1998; Gasco et al., 1999; Kriwet and Muller-Goymann, 1995; Trotta, 1999; Sheela et al., 2012).

For transdermal distribution of indomathacin, Barakat et al used the spontaneous emulsification approach to make nanoemulsions (Barakat et al., 2011). In comparison to the typical indomethacin gel, nanoemulsion formulations showed a considerable increase in permeability characteristics such as steady-state flow, permeability coefficient, and enhancement ratio. When compared to a standard indomethacin gel, nanoemulsion formulations demonstrated a considerable increase in percent inhibition value after 4 hours on carrageenan-induced paw edoema in rats. Nanoemulsion formulations showed a significant increase in permeability metrics (P<0.05). The steady-state flux and permeability coefficient for the improved nanoemulsion formulation (reported to be 22.61 ± 3.45 µg/ cm2 /h and 0.22x10-2 ± 0.0003 cm/h, respectively) were significant when compared to standard indomethacin gel (P<0.001). When compared to indomethacin gel, the enhanced ratio was determined to be 8.939 in improved formulation. These findings suggested that nanoemulsions could be utilised as vehicles for enhanced transdermal administration of indomethacin, perhaps eliminating the oral dose's adverse effects.

To improve the drug's water solubility and bioavailability, Singh et al created a nanoemulsion formulation for transdermal delivery of carvedilol (Singh et al., 2012). The spontaneous emulsification approach was used to make O/W nanoemulsions. Plasma carvedilol was elevated 6.41 times to the marketed dose form after application. According to the findings, nanoemulsion dramatically increased the bioavailability of carvedilol when applied transdermally and eliminated first-pass metabolism.

Sajid et al., (2013) used an aqueous phase titration method to make betamethasone valerate nanoemulsions with Sefsol, Tween 20, Transcutol P, and distilled water as the oil phase, surfactant, co surfactant, and aqueous phase, respectively, and evaluated them based on the induction of contact dermatitis in rats using a dispersion of nickel sulphate in solid vaseline at 5%, Carbopol 934 was used to transform the optimised nanoemulsion into a hydrogel. The average drug deposition in skin was 58.46 µg/cm2. In vivo anti-inflammatory activity of the created nanoemulsion gel and commercialised cream showed 84.2 percent and 45.05 percent suppression of inflammation, respectively. The irritation score was determined to be 1.83, indicating that the improved nanoemulsion caused no irritation. The contact dermatitis model revealed that the nanoemulsion formulation gel did not appear to generate an inflammatory or immunological response.

Huafeng et al., (2010) conducted research to develop a lecithin nanoemulsion as a topical delivery vehicle without the use of synthetic surfactants and to assess its topical delivery capacity. Experiments showed that as the concentration of soybean lecithin and glycerol increased, the size of the lecithin nanoemulsion droplet shrank and the viscosity increased. When lecithin nanoemulsion was put into o/w cream, it considerably increased the cream's skin hydration capacity, with a 2.5-fold increase when the concentration of lecithin nanoemulsion reached 10%. When an o/w cream containing Nile-red-loaded lecithin nanoemulsion was applied to the abdominal skin of a rat in vivo, it was shown to increase the penetrability of Nile red dye into the dermis layer. In the dermis layer that had received the cream with a Nile red-loaded lecithin nanoemulsion, the arbitrary unit of fluorescence was around 9.9-fold higher than the cream with a Nile red-loaded general emulsion. These findings show that lecithin nanoemulsion could be a potential lipophilic chemical topical delivery mechanism.

Modi et al looked into the possibilities of a nanoemulsion formulation for aceclofenac topical delivery (Modi and Patel, 2011). The improved formulations' in vitro skin penetration profile was compared to that of aceclofenac conventional gel and nanoemulsion gel. In an optimised nanoemulsion formulation containing 2% w/w aceclofenac, 10% w/w Labrafac, 45 percent w/w surfactant mixture (Cremophor® EL: Ethanol), and 43 percent w/w distilled water, permeability parameters such as steady-state flux, permeability coefficient, and enhancement ratio increased significantly. When compared to aceclofenac conventional gel and nanoemulsion gel on carrageenan-induced paw edoema in rats, the anti-inflammatory effects of formulation exhibited a substantial increase in percent inhibition value after 24 hours. These findings suggested that nanoemulsions could be used to increase aceclofenac transdermal distribution.

Batoota et al looked at the use of nanoemulsion formulations for celecoxib transdermal delivery (Baboota et al., 2007). The improved formulations' in vitro skin penetration profile was compared to celecoxib gel and nanoemulsion gel. In nanoemulsion formulations, there was a significant increase in steady state flow, permeability coefficient, and enhancement ratio (p<0.05). The formulation with the highest value of these permeability characteristics had 2% (w/w) celecoxib, 10% (w/w) oil phase (Sefsol 218 and Triacetin), 50% (w/w) surfactant mixture (Tween-80 and Transcutol-P), and 40% (w/w) water. The formulation's antiinflammatory effects on carrageenan-induced paw edoema in rats exhibited a substantial increase (p<0.05) in inhibition after 24 hours when compared to celecoxib gel and nanoemulsion gel. These findings suggested that nanoemulsions could be used to increase celecoxib transdermal distribution.

Harwansh et colleagues investigated an isotropic and thermodynamically stable nanoemulsion formula for transdermal distribution of glycyrrhizin with low surfactant and cosurfactant concentrations to improve solubility, permeation enhancement, and stability (Ranjit et al., 2011). The optimised nanoemulsion formulation, which included 1 percent w/w mono ammonium glycyrrhizinate, 32.4 percent Span 80, 3.7 percent Brij 35, 10% isopropyl alcohol, 46.5 percent soyabean oil, and 6.4 percent distilled water, showed a significant increase in permeability parameters such as steady-state flux and permeability coefficient. The gel and nanoemulsion formulations investigated showed no signs of skin irritation. Because nanoemulsions' excipients operate as permeation enhancers, the results showed that nanoemulsions are potential vehicles for transdermal administration of glycyrrhizin through human cadaver skin without the use of additional permeation enhancers.

For transdermal distribution of tamoxifen citrate for breast cancer, Inayat and Setty (2011) created a nanoemulsion formulation. The Keshary-Chien diffusion cell was used to assess the transdermal penetration of tamoxifen citrate via rat skin. The optimised nanoemulsion formulation, which contains 5% w/w of medication, 4.12% w/w of oil phase, 37.15 percent w/w of surfactant (mix), and 58.73 percent w/w of distilled water, showed a considerable increase in permeability parameters such as steady–state flow. It had a globule size of 68 nm on average. Transmission electron microscopy confirmed spherical particle morphology, whereas DSC and FTIR analysis revealed ingredient compatibility. These findings suggested that the produced system would be useful for improving tamoxifen citrate transdermal efficacy.

The potential of a nanoemulsion formulation for transdermal administration of aceclofenac was examined by Shakeel et al., (2007). The Franz diffusion cell was used to assess the transdermal penetration of aceclofenac via rat abdomen skin. The improved formulations' in vitro skin penetration profile was compared to that of aceclofenac conventional gel and nanoemulsion gel. The optimised nanoemulsion formulation, which contained 2% w/w of aceclofenac, 10% w/w of Labrafil R, 5% w/w of Triacetin R, 35.33 percent w/w of Tween 80 R, 17.66 percent w/w of Transcutol PR, and 32 percent w/w of distilled water, showed a significant increase in permeability parameters such as steady-state flux, permeability coefficient, and enhancement. When compared to aceclofenac conventional gel and nanoemulsion gel on carrageenan-induced paw edoema in rats, the anti-inflammatory effects of the optimised formulation revealed a substantial increase in percent inhibition value after 24 hours. These findings suggested that nanoemulsions could be used to increase aceclofenac transdermal distribution.

Shakeel et al., (2012) provided an overview of the efforts made by numerous researchers over the previous decade in researching novel forms of nanoemulsion-based drug delivery systems for cutaneous and transdermal distribution of several hydrophobic substances. This area of research would be extremely beneficial to formulation scientists in order to develop nanoemulsion-based formulations for commercial and clinical uses. Furthermore, Harwansh et al examined several researchers' efforts in nanoemulsion delivery of phytophar maceuticals (Ranjit et al., 2011).

**45.4.10. Cancer therapy and targeted drug delivery using nanoemulsion**

The use of nanoemulsion formulations for controlled medication administration and targeting (Wang et al., 2007) is another intriguing application that is currently under research. They can easily be targeted to the tumour location due to their submicron size. Although nanoemulsions are most commonly used to transport water insoluble pharmaceuticals, they have lately gained popularity as colloidal carriers for the targeted delivery of anticancer treatments, photosensitizers, neutron capture therapy agents, and diagnostic agents. The development of magnetic nanoemulsions is a novel cancer therapeutic method. Photosensitizers like Foscan® can be delivered to deep tissue layers across the skin, causing hyperthermia and subsequent free radical production. Photodynamic therapy (Primo et al., 2007) is a type of this technology that can be used to treat cancer.

**45.4.11. Intranasal medication delivery with nanoemulsions**

In addition to parenteral and oral methods, the intranasal drug delivery system is currently regarded as a dependable route for drug administration. The nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic medicines, as well as a promising means to circumvent the barriers to direct drug entrance to the target site (Pires et al., 2009). This method is also non-invasive, painless, and highly tolerated. Because of its low enzymatic activity, great availability of immunoactive sites, and fairly permeable epithelium, the nasal cavity is one of the most efficient sites (Ugwoke et al., 2005). There are various issues with targeting pharmaceuticals to the brain, particularly hydrophilic and high molecular weight drugs. This is due to the endothelium's impervious nature, which separates the systemic circulation and acts as a barrier between the blood and the brain (Pardridge, 1999). The olfactory region of the nasal mucosa provides a direct link between the nose and the brain, and disorders including Alzheimer's disease, migraine, depression, schizophrenia, Parkinson's disease, meningitis, and others can be treated with nanoe mulsions laden with medications (Kumar et al., 2008; Mistry et al., 2009). It has been claimed that nanoemulsions containing risperidone can be prepared for delivery to the brain via the nose (Csaba et al., 2009). The nasal route is thought to be more successful than the intravenous method for this emulsion. Another therapeutic application of intranasal drug delivery systems is the production of vaccinations. The delivery of mucosal antigen results in immunity. The first intranasal vaccine is currently on the market (Csaba et al., 2009). Using nano-based carriers to protect biomolecules, improve nanocarrier contact with mucosae, and direct antigen to lymphoid tissues is one of the most promising delivery technologies. As a result, the use of nanoemulsions in intranasal drug delivery systems is expected to yield considerable results in medication targeting to the brain in the treatment of central nervous system illnesses (Clark et al., 2001). For sustained action, Bhanushali et al., (2009) produced intranasal nanoemulsion and gel formulations for rizatriptan benzoate. To create thermo-triggered mucoadhesive nanoemulsions, various mucoadhesive agents were tested. Different ratios of HPMC and Carbopol 980 were used to make rizatriptan mucoadhesive gel formulations. A comparison of intranasal nanoemulsions and intranasal mucoadhesive gels revealed that nanoemulsions could achieve better brain targeting. Insulin and testosterone (Tamilvanan, 2004) are two more medications that have been designed for nasal administration.

**45.4.12. Parenteral medication delivery and nanoemulsions**

This is one of the most popular and successful drug delivery methods for actives with low bioavailability and a narrow therapeutic index. Nanoemulsions are good carriers for parenteral delivery because of their ability to dissolve vast amounts of hydrophobics, as well as their mutual compatibility and ability to protect medicines from hydrolysis and enzymatic destruction. Furthermore, because these emulsions ensure the continuous and controlled release of medications over lengthy periods of time, the frequency and dosage of injections can be lowered during the drug therapy period. Furthermore, the lack of flocculation, sedimentation, and creaming, as well as a large surface area and free energy, provide clear advantages over bigger particle size emulsions for this mode of administration (Ravi and Padma, 2011). Their vast interfacial area has a good impact on medication transport and distribution, as well as targeting specific areas. Parenteral nanoemulsion-based carriers have therefore been used in major clinical and pre-clinical research. Patel and Patel (Patel and Patel, 2010) examined the advancements in these innovative medication delivery methods. Nanoemulsions containing thalidomide have been developed, and plasma concentrations as low as 25 mg have been found to be therapeutic (Araujo et al., 2011). However, after two months of storage, the drug content of the nanoemulsion decreased significantly at 0.01 percent drug formulation, which might be overcome by adding polysorbate 80. Breast and ovarian cancer have been treated with chlorambucil, a lipophilic anticancer drug. Its pharmacokinetics and anticancer activities were investigated by putting it into parenteral emulsions made with high-energy ultrasonication. In mice with colon adenocarcinoma, therapy with this nanoemulsion results in a better tumour suppression rate than treatment with plain drug solution, indicating that the drug-loaded emulsion could be an efficient carrier for drug delivery in cancer treatment (Ganta et al., 2010). Because of its poor water solubility, carbamazepine, a frequently used anticonvulsant medication, had no parenteral treatment available for patients. Kelmann et al., created a nanoemulsion for intravenous administration that demonstrated good in vitro release kinetics (Kelmann et al., 2007). Diazepam, propofol, dexamethasone, etomidate, flurbiprofen, and prostaglandin E1 have all been observed in parenteral nanoemulsion formulations (Brussel et al., 2012).

Because of the high lipophilicity of diazepam (an anxiolytic and sedative), it is necessary to use solvents (such as propylene glycol, phenyl carbinol, and ethanol) to dissolve the drug in traditional aqueous preparations (Valium® and Stesolid®), resulting in pain and thrombophlebitis in the patient during the injection. The development of a nanoemulsion, commercially available under the name of Diazemuls® (Kabi-Pharmacia) allows for the reduction of these adverse effects, keeping stages of distribution and elimination similar to Valium®. However, higher doses of Diazemuls® are necessary to obtain the same effect as Valium® since this leads to higher free fraction of plasma diazepam (Gleeson et al., 1983; von Dardel et al., 1983).

Due to stability issues, the solution for intravenous administration of etomidate (hypnotic short) comprises 35 percent propylene glycol (Hypnomidate®) (Doenicke et al., 1999; Nyman et al., 2006). Because of the solvent's high osmolarity, administration has been linked to a variety of side effects, including hemolysis, thrombosis, thrombophlebitis, and pain at the application site (Doenicke et al., 1997; Nebauer et al., 1992). Lipuro-etomidate® (B. Braun) is a nanoemulsion containing 2 mg/ml Lipofundin® etomidate in medium chain triglyceride (Doenicke et al., 1990). Aside from the pain at the time of administration, the emulsion allowed for a reduction in hemolytic and venous sequelae (Doenicke et al., 1999; Nyman et al., 2006; Doenicke et al., 1997).

Propofol (anaesthetic) has complicated pharmacokinetics and pharmacodynamics. It has a quick initial distribution of around 2-3 minutes, with considerable variability across patients and subtherapeutic values within minutes. However, because of its high lipophilicity, it has a large volume of distribution and can take days to completely eliminate from the body (Calvo et al., 2004). Because of the anaphylactic reactions associated with Cremophor EL, which was present in the original formulation of propofol nanoemulsion as a vehicle for this drug, which contained soybean oil, glycerol, egg yolk lecithin, and disodium edentate, this vehicle helped to reduce the volume of distribution of the drug, speeding up clearance processes by the responsible agencies. Apart from the pharmacokinetic characteristics of the drug (Calvo et al., 2004) and the differences in each patient's lipoprotein profile due to propofol's high binding to low density lipoprotein and albumin (Schicher et al., 2008), the various generic formulations currently available are characterised by an additional factor of variability in response between individuals in the induction of anaesthesia. Some changes in the formulation of Diprivan® adverse effects have been proposed, including some already being marketed as Propofol® Lipuro (B. Braun) as an oil core that contains a mixture of oils (Ward et al., 2002), due to related pain at the injection site and increased triglyceride levels after administration for long periods of time. Due to enhanced drug incorporation in the oily core and a smaller amount of free propofol phase in the exterior aqueous emulsion, adding more oil to the formulation reduced discomfort on injection (Doenicke et al., 1997; Schicher et al., 2008; Ward et al., 2002; Rau et al., 2001; Knibbe et al., 1999). Alternative formulations have been created, such as incorporating higher propofol concentrations (6%) in the nanoemulsion (Knibbe et al., 1999; Cox et al., 1998; Knibbe et al., 2004) or developing a propofol prodrug in solution (Aquavan®) (Fechner et al., 2008).

Moreover, despite dexamethasone's outstanding anti-inflammatory properties, the therapeutic usage of corticosteroids is limited by a slew of adverse effects (Panyam and Labhasetwar, 2004; Yokoyama and Watanabe, 1996). Lipophilic prodrugs in the body that are gradually hydrolyzed to the active metabolite can be employed to overcome these difficulties (thus presenting prolonged anti-inflammatory effect). The benefit is that smaller doses are utilised than in the traditional water soluble version (dexamethasone phosphate), lowering the likelihood of side effects. Because it is picked up by inflammatory cells of the mononuclear phagocytic system, nanoemulsions were used as a vehicle for the lipophilic prodrug of dexamethasone (palmitate), which is commercially available as Limethason® (Green Cross Co./Mitsubishi Tanabe Pharma Co.). Rheumatoid arthritis, West syndrome, inflammatory disorders, and other autoimmune diseases all responded well to Limethason® treatment. While dexamethasone phosphate solution is readily dispersed in water-rich tissues like muscles, the nanoemulsion accumulates mostly in inflammatory organ tissues like the liver and spleen. Even if the elimination pattern is identical, the biodistribution profile is distinct. At a dosage of 0.03 mg/mL, limethason® inhibits macrophage phagocytic activity by approximately 80% (Yokoyama and Watanabe, 1996).

Rheumatoid arthritis and other inflammatory illnesses linked or not with cancer are treated with flurbiprofen (non-steroidal anti-inflammatory oral usage), a lipophilic medication (Kumpulainen et al., 2010). Because of the drug's lack of oral availability and/or numerous gastrointestinal side effects, it is frequently administered by parenteral route. Because of the severe local irritation caused by the sodium salt of flurbiprofen, it was developed as a flurbiprofen prodrug (cefuroxime), and because of the latter's lipophilicity, it was incorporated into nanoemulsions for parenteral use (Ropion®, Kaken Pharmaceuticals Co., Lipfen®, GreenCross Co.), and has been commercially available in Japan since 1992. When compared to the solution, Ropion® caused an increase in the area under the concentration-time curve and a decrease in clearance. Due to decreased absorption by the mononuclear phagocyte system, drug inclusion into nanoemulsions including unesterified ethyl oleate, lecithin, and modified egg yolk resulted in lower drug accumulation in organs such as the liver and spleen (Brussel et al., 2012).

Prostaglandin E1, which is produced in multiple locations throughout the body, is responsible for a variety of physiological effects including vasodilation, blood pressure reduction, angiogenesis, and platelet aggregation inhibition (Hoshi, 1996; Igarashi et al., 2001). It has a short half-life when used to treat many disorders, necessitating high doses, which can cause a variety of side effects including hypotension, diarrhoea, local irritation, and discomfort (Hoshi, 1996). PGE1 complexed to cyclodextrins was commercially accessible in 1975, and prostaglandin E1 was included in lipid nanoemulsions in 1985 (Liple®, Mitsubishi Tanabe Pharma Corporation, Palux®, Taisho Pharmaceutical) (Momma, 1996). Because lipid formulations accumulate in the walls of wounded arteries, they deliver drugs to the site of vascular injury and protect them from fast inactivation by the lungs (Hoshi, 1996; Igarashi et al., 2001; Momma, 1996; Scheffler et al., 1996).

**45.4.13. Nanoemulsions and medication delivery in the lungs**

Due to noninvasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a large surface area for local drug action and systemic absorption of drug, the lung is an attractive target for drug delivery. In pulmonary drug delivery, colloidal carriers (ie, nanocarrier systems) have several advantages, including the ability to achieve relatively uniform drug dose distribution among the alveoli, improved drug solubility from its own aqueous solubility, sustained drug release, which reduces dosing frequency, improves patient compliance, reduces side effects, and the potential for drug internalisation by cells (Heidi et al., 2009). The submicron emulsion technology has not been effectively utilised for pulmonary drug delivery until recently, and there has been relatively little published in this area (Heidi et al., 2009). Bivas-Benita et al., reported that cationic submicron emulsions are promising carriers for deoxyribonucleic acid vaccines to the lung because they can transfect pulmonary epithelial cells, possibly causing cross priming of antigen-presenting cells and directly activating dendritic cells, resulting in antigen-specific T-cell stimulation (Bivas-Benita et al., 2004). As a result, nebulization of submicron emulsions will be an emerging research field. However, due to the potential for deleterious effects of surfactants and oils on lung alveoli function, substantial research is required for the successful creation of inhalable submicron emulsions (adverse interactions with lung surfactant). Using lecithin-stabilized microemulsions synthesised in trichlorotrifluoroethane, a novel pressurised aerosol system for the pulmonary administration of salbutamol has been developed (Lawrence and Rees, 2000).

**45.4.14. Nanoemulsions as a carrier for gene delivery**

Emulsion systems have been used as an alternative to liposomes as gene transfer vectors (Liu et al., 1996). Other emulsion investigations for gene delivery (non-pulmonary route) have found that the emulsion/DNA combination binds to the DNA more strongly than liposomal carriers (Yi et al., 2000). Genes were supplied more efficiently by this stable emulsion approach than by liposomes (Liu and Yu, 2010). The effect of the stearylamine inclusion phase (water or oil), the time of complexation, and various incubation temperatures was investigated. Electrophoresis migration on a 0.7 percent agarose gel was used to determine the complexation rate, and dynamic light scattering was used to characterise the nanoemulsion and lipoplex (DLS). The results show that the optimal DNA compaction occurs after 120 minutes of complexation, at a low temperature (4 ± 1 °C), and after the cationic lipid is incorporated into the aqueous phase. Although lipoplexes' zeta potential was lower than that of simple nanoemulsions, the granulometry remained same. Furthermore, lipoplexes have been shown to be effective carriers for gene transfer.

**45.5. Phytopharmaceutical nanoemulsions**

The development of innovative drug delivery systems for herbal medications has received a lot of interest recently (Saraf, 2010). However, due to limitations in plant bioactives such as instability in strongly acidic pH and liver metabolism, drug levels in the blood were below therapeutic concentrations, resulting in a reduced or non-therapeutic impact (Goyal et al., 2011). As a result, encapsulating plant extracts or their bioactives reduces their degradation or presystemic metabolism, as well as major adverse effects from drug buildup in non-targeted locations, and makes administration easier in juvenile and elderly patients (Uhumwangho and Okor, 2005). In comparison to conventional formulations such as conventional emulsions, lipid nanoemulsions containing oil from medicinal plants or hydrophobic drugs have been shown to improve drug solubility, reduce side effects of various potent drugs, increase drug bioavailability, and prolong pharmacological effects (Youenang-Piemi et al., 1999). It has been claimed that phytoactive nanoemulsions can be made.

In vivo, the effect of nanoemulsion on colchicine absorption was observed. Isopropyl myristate, eugenol, Tween 80, ethanol, and water were used to make a colchicine nanoemulsion, with eugenol serving as the oil phase. The nanoemulsion formulation considerably increased intestinal absorption of colchicine, according to the results (Shen et al., 2011). Although genistein has been demonstrated to have anticancer properties in various experimental settings, its poor bioavailability has prevented it from being incorporated into clinical practise. Researchers have explored a variety of nano methods, including spontaneous emulsification of genistein into topical nanoemulsion formulations with egg lecithin, medium chain triglycerides, or octyldodecanol and water (Silva et al., 2009). Curcumin's antiinflammatory efficacy was also boosted in oil in water nanoemulsion formulation (Wang et al., 2008).

**45.6. Future possibilities**

Because of their ability to solubilize non-polar active chemicals, nanoemulsions have been proposed for a variety of uses in pharmacy as drug delivery devices. Future applications of nanoemulsions in treatments and cosmetics development for hair and skin are particularly promising. Nanoemulsions have a wide range of uses, including medication delivery, where they operate as efficient carriers for bioactives and facilitate administration via multiple routes. The advantages and applications of nanoemulsions for oral medication delivery are numerous, with droplet size being connected to gastrointestinal absorption. Nanoemulsion may be the optimal delivery platform for these difficult-to-formulate phytopharmaceuticals, given the growing interest in herbal medication formulation. The future of nanoemulsions is dependent on the capacity of formulation specialists to use the advantages of nanoemulsion carriers to overcome unique drug delivery challenges such as absorption, penetration, and stability of both orthodox and herbal medications.

**45.7. Conclusion**

Nanoemulsions provide a number of advantages for medication delivery and are consequently gaining popularity as drug carriers for boosting active medicinal ingredient delivery. They are suitable to practically all delivery routes and hence show promise in a variety of sectors, including cosmetics, pharmaceuticals, and biotechnology. This novel method could be used to overcome some phytopharmaceuticals' low absorption as well as their poor miscibility with the lipid contents of cell membrane linings.

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