Nanoemulsions Challenges and Future Prospects as a Drug Delivery System

Farzad Abaszadeh, Muhammad Hossein Ashoub, and Mahnaz Amiri

Abstract Nanoemulsion during the recent years proved that has the potential to overwhelm numerous difficulties in formulation of drugs. By loading drugs with poor water-solubility in the proper nanoemulsions improves their solubility and/or wettability. Therefore, this expands their pharmacodynamics as well as pharmacokinetics by diverse administration methods. Accompanying with the optimal size of nanodroplets, the droplets act as a drugs pool, facilitating nanoemulsion to do as a multifunctional platform to defect different diseases. A number of significant advantages, which include nanoemulsion qualities, such as well-organized drug release with suitable rate, extended efficacy, control of drug uptake, the ability of drug protection from oxidation and low side effects, have been described in last decades. The great characteristic of nanoemulsion contains also a diversity of engineering procedure options as well as a combination of extensively mixed components such as liquid lipids, surfactants or even drug-conjugates. These structures afford alternatives for designing advanced nanoemulsions pointing at high-value and different applications. This review presents the challenges and prospects of diverse nanoemulsion types and its application as drug delivery methods. Types of nanoemulsions as well as components of a nanoemulsions, their manufacturing via different methods like (High pressure homogenization, Ultrasonication, Microfluidization, Phase Inversion, Temperature Spontaneous Emulsification, Membrane Emulsification, Emulsion Inversion Point) is described. Different drug delivery applications (Oral, Parenteral, Transdermal, Topical, Intranasal and Ocular delivery) is presented. Kinetics of drug release as well as stability of nanoemulsions are also presented.

Keywords Drug delivery system · Nanoemulsion · Manufacturing · Applications

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A. Husen et al. (eds.), *Current Trends in Green Nano-emulsions*, Smart Nanomaterials Technology, https://doi.org/10.1007/978-981-99-5398-1_13

List of abbreviations

(BCS)	Biopharmaceutics Classification System
(BBB)	Blood Brain Barrier
(CNS)	Central Nervous System
(DLVO)	Derjaguin, Landau, Verwey, And Overbeek
(DOPE)	Di-Oleoyl Phosphatidylethanolamine
(DSPC)	Di-Stearoyl Phosphatidylcholine
(EIP)	Emulsion Inversion Point
(FDA)	Food and Drug Administration
(GIT)	Gastrointestinal Tract
(GRAS)	Generally Recognized as Safe
(HPH)	High-Pressure Homogenization
(HLB)	Hydrophilic-Lipophilic Balance
(IV)	Intravenous
(IPM)	Isopropyl Myristate
(LC)	Liquid Chromatography
(MQ)	Methyl Quercetin
(O/W)	Oil-In-Water
(O/W/O)	Oil-In-Water-In-Oil
(PIT)	Phase Inversion Temperature
(PEG)	Polyethylene Glycol
(POE)	Polyoxyethylene
(Ph)	Potential of Hydrogen
(W/O)	Water-In-Oil
(W/O/W)	Water-In-Oil-In-Water

1 Introduction

Pharmaceutical dosage forms have evolved from very basic to extremely sophisticated systems, sometimes referred to as new drug delivery systems, due to technological advancements. With mean droplet sizes generally ranging from roughly 50 to 500 nm in pharmaceutical applications, nano-emulsion-based delivery systems typically consist of a colloidal dispersion of oil and water phases [6–9]. Oil-in-water (O/W) or water-in-oil (W/O) nano-emulsions are possible, where the droplets are made of either oil or water. To stabilize nano-emulsions, pharmaceutically approved surfactants that are regarded as safe (generally recognized as safe (GRAS)) are utilized as emulsifiers. Nano-emulsions are especially excellent medication delivery methods because of their ability to dissolve vast amounts of insufficiently water-soluble medicines while also shielding them from deterioration. Increased drug loading, higher drug solubility, enhanced bioavailability, chemical or enzymatic degradation

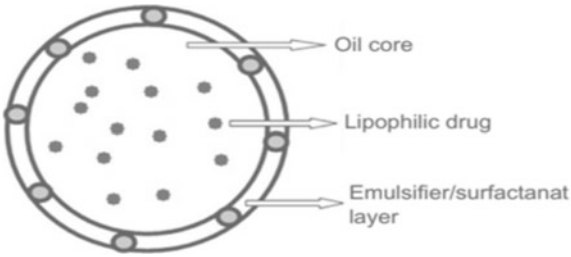

Fig. 1 An illustration of the O/W Nano-emulsion system [55]

resistance, and controlled drug release are among the main benefits of nano-emulsions for this use [31].

Additionally, the wide interfacial area and tiny droplet size may improve the targeted administration of bioactive substances. Nano-emulsions also exhibit other intriguing physicochemical characteristics, including exceptional optical clarity and peculiar viscoelastic behavior, as a result of the comparatively small size of the droplets. Nano-emulsions can have rheological qualities that range from liquid to semisolid and optical properties that range from opaque to almost transparent. It should be noted that a variety of distinct colloidal dispersions with some comparable and some different properties may be created from oil, water, and surfactants (Fig. 1). The dispersed droplets can be divided into three types, depending on their size and thermodynamic stability: (i) Micro emulsions, (thermodynamically stable and diameters between 20 and 100 nm); (ii) Nano-emulsions, (metastable stables and mean particle diameters under 200 nm); and (iii) conventional emulsions (metastable systems and mean particle diameters between 200 nm and several micrometers) [49].

A biphasic liquid system is an emulsion in which one liquid's internal or dispersed phase is scattered as tiny droplets across the exterior or continuous phase of the other liquid. Numerous physicochemical elements have been shown to impact how emulsion nanoparticles behave in living things (Fig. 2). For novel emulsion nanomedicines to treat illness and adhere to strict regulatory standards effectively; these aspects must be regulated. Size is a crucial physical factor that affects how cells react to nanoparticles. The renal and reticuloendothelial systems quickly remove somewhat bigger nanoparticles, >60 nm, and smaller, <20 nm. Nanoparticles with a size of approximately 50 nm have the maximum cellular uptake. As nanoparticle size increases, different cellular uptake pathways are used: small nanoparticles (200 nm or smaller) are taken up via pinocytosis pathways, those between ~250 nm and larger are absorbed by phagocytosis, and those larger than microns are taken up by non-receptor mediated micropinocytosis [27]. For the Food and Drug Administration (FDA) to approve nanomedicine, size distribution, a measurement of the various populations of each size, is becoming more and more crucial. Contrary to polydisperse droplet systems, formulations with monodisperse emulsion droplets exhibit predictable as well as repeatable biological activity. This demonstrates how essential emulsion stability against coalescence is the stability of emulsions against coalescence, as well as their interactions with biological tissues, are governed by their surface characteristics. It is well known that extracellular proteins cover nanoparticle surfaces

when injected into the body. The precise surface characteristics of the nanoparticle have a significant role in determining the composition of this layer, known as the "protein corona". The surface charge is crucial in controlling the protein corona and subsequent interactions with cells. Due to electrostatic repulsion, anionic nanoparticle surfaces are not easily absorbed via cells and are often quickly eliminated by liver and macrophage cells [45]. Although cationic nanoparticle surfaces readily attach to the negatively charged cell surface, increasing absorption, there was still an enhanced clearance problem because of opsonization and macrophage uptake. Coating nanoparticles can obtain similar results with hydrophilic uncharged polymers, such as Polyethylene Glycol (PEG), which act as a steric barrier to protein adsorption and lessen electrostatic attraction [23]. A Nano medicine formulation's unique requirement must be carefully considered while choosing a suitable emulsion excipient. To comply with FDA regulations, the excipient must rapidly solubilize the problematic medicine, be non-toxic, biocompatible, and produce monodisperse stable emulsion droplets [73].

A perfect medication delivery system achieves the goal of increasing therapeutic impact while reducing toxicity. With the passage of time and the development of science and technology, dosage forms have changed from straightforward mixes and tablets to incredibly complex systems known as innovative drug delivery systems. The medication delivery technique known as nano-emulsions is one such example.

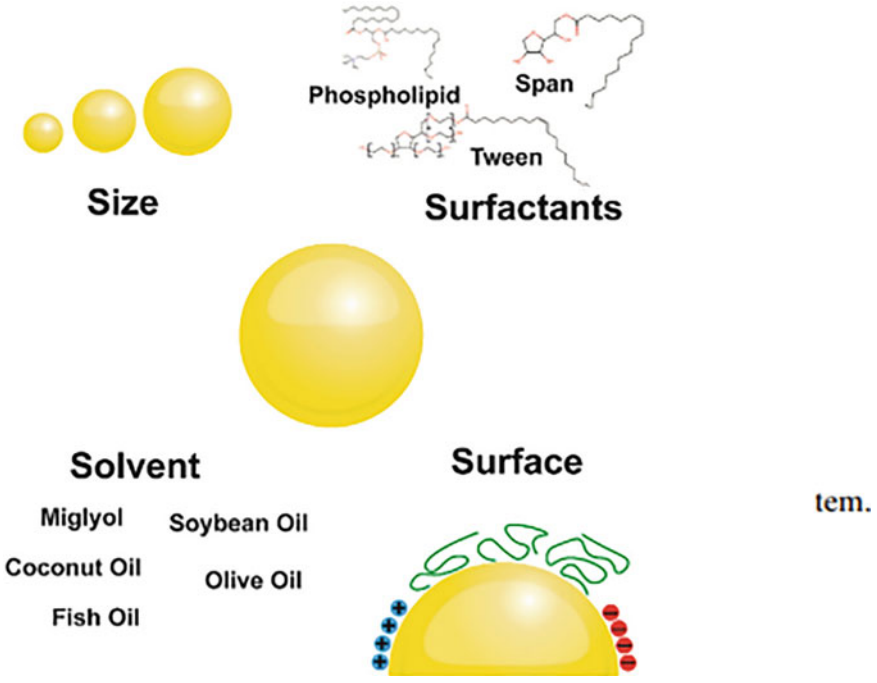

Fig. 2 Systematic drug distribution using Nano-emulsion [81]

The term "nano-emulsion" refers to a dispersion of two immiscible liquids, such as oil and water, which is thermodynamically stable, isotropically transparent, and stabilized by an interfacial surfactant coating. Nano-emulsions have a uniform, tiny droplet sizes between 20 and 200 nm. Nano-emulsions do not form naturally; external shear is required to separate larger droplets into smaller forms. Compared to microemulsion phases, there isn't much information available about making and managing nano-emulsions. The first nano-emulsions were created in the 1940s and can be classified as bi-continuous, (O/W) or (W/O). Nano-emulsions are also called mini emulsions, submicron emulsions, and ultrafine emulsions. Research shows that nano-emulsion is a far more effective medication delivery than other transdermal drug delivery systems. Although emulsion is thermodynamically unstable but kinetically stable, the primary physical distinction between emulsion and nano-emulsion is that the former is murky while the latter is quite transparent [13–15, 51].

2 Types of Nano-Emulsions

A fine dispersion of pharmaceuticals in nanodroplets makes up a nano-emulsion, an isotropic, transparent, or translucent, heterogeneous system of two immiscible liquids. An interfacial layer of emulsifiers and co-emulsifiers stabilizes it. With small droplet sizes (20 to 400 nm), a uniform size distribution, and various physicochemical and biological properties from other emulsions (>500 nm), they are thermodynamically and kinetically stable systems. The two immiscible phases are often supplemented with substances soluble in either oil or water. In the presence of an emulsifier, mixing oil and water results in a coarse emulsion that can spontaneously transform into a nano-emulsion or be made using high energy [28, 61, 64, 68, 69]. In their simplest form, emulsions consist of two phases, one of which is hydrophilic and the other of which is hydrophobic (Fig. 3). These emulsions are therefore named as (O/W) emulsions, where small oil droplets are scattered through water, or (W/O) emulsions, where small water droplets are disseminated through oil. However, by enclosing an emulsion within an emulsion named as a double emulsion and creating water-in-oil-in-water (W/O/W) or oil-in-water-in-oil (O/W/O) emulsions, more complexity may be added to these straightforward systems. In the past, creating double emulsions required creating an initial internal emulsion, which was encircled via creating a second emulsion on top of the initial emulsion. Double emulsions provide extra difficulties in their formation and stabilization, including the need for lipophilic and hydrophilic surfactants to stabilize each oil–water interface and a higher propensity for degradation and coalescence because of diffusion between the phases. Rekindled research interest has been shown in uniform double emulsions produced by microfluidic devices for use as microreactors or templates for particle production [42, 53].

Oil, water, and a surfactant make up typical nano-emulsions. Choosing the suitable surfactant is essential for creating and maintaining nano-emulsions. Nano-emulsions are kinetically stable but thermodynamically unstable. In other words, nano-emulsion

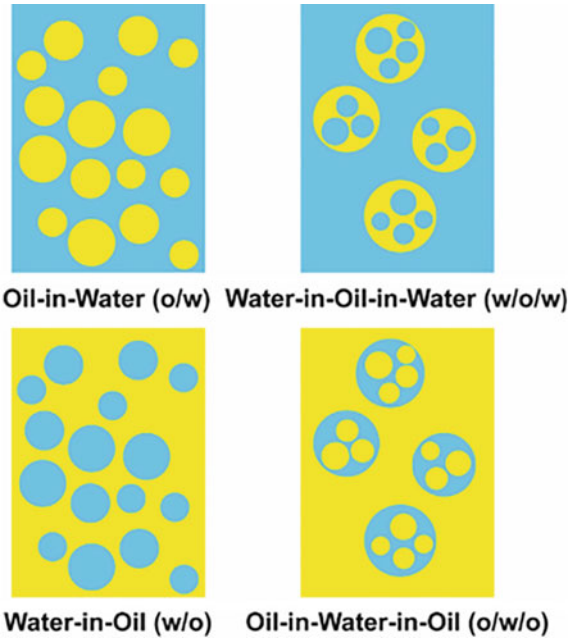

Fig. 3 Emulsion forms are divided into continuous and scattered phases [81]

phase separation happens with enough time. For use in a variety of pharmacological, culinary, and cosmetic applications, nano-emulsions have been produced. They must be toxic-free and biocompatible for all of these purposes. As a result, choosing the right oil and surfactants is crucial. It is preferable to use biocompatible oils and surfactants, such as vegetable or pharmaceutical-grade oils. In addition to surfactants, proteins and lipids are frequently utilized to stabilize nano-emulsions. As it solubilizes lipophilic medications intended to be utilized for a variety of diseases, the oil phase is crucial in the formation of nano-emulsions. Depending on the administration location, the quantity of oil in an o/w type nano-emulsion can range from 2 to 20% w/w. According to Choudhury et al. [18], Biopharmaceutics classification system (BCS) classes II and Intravenous (IV) medications are the best options for creating o/w nano-emulsions since they help increase the solubility of the pharmaceuticals. Isopropyl Myristate (IPM), Triacetin (Glyceryl triacetate), Sefsol 218 (Propylene glycol mono ethyl ether), etc., are among the FDA-approved and GRAS-certified oils that are favored over traditional high-density fixed oils like castor oil, coconut oil, sesame oil, cottonseed oil, fish oil, linseed oil, mineral oil, olive oil, peanut oil, and sunflower oil [18, 19, 76]. Based on their solubility and emulsification power, the top emulsifier systems are chosen from a pool. Due to the less toxicity and irritating than their anionic, and especially their cationic counterparts, non-ionic surfactants are frequently applied. Emulsifiers are chosen based on the solubility in aqueous and oil phases, hydrophilic-lipophilic balance (HLB) value, and lower toxicity, among others. Non-ionic surfactants with an HLB value of 8–16 is ideal for creating an o/w nano-emulsion.

Depending on the composition, three types of nano-emulsions are most likely to form:

- Water with oil where Oil droplets spread in a continuous aqueous phase in nano-emulsions
- Water in a liquid nano-emulsions in which the continuous oil phase is diluted with water droplets
- Bi-continuous Nano-emulsions, in which the system contains interspersed microdomains of water and oil [12, 38, 75].

3 Components of a Nano-Emulsion

Oil: Oil is the second most important carrier after water due to its capacity to solubilize lipophilic medication compounds and improve absorption toward the body's lipid barrier. Due to its exceptional capability to penetrate cell walls, oil is beneficial for administering lipophilic active drugs (Fig. 4).

Surfactant: To aid in the dispersion of all components, the surfactant has to be capable of reducing the interfacial tension as near to zero as possible. When making a W/O nano-emulsion, Surfactants with HLB values between 3–6 are beneficial, however surfactants with increased HLB values between 8 and 18 are useful for making O/W nano-emulsions. Surfactants with an HLB value of 20 or higher operate as co-surfactants to lower surfactant levels to acceptable levels and create microemulsions. The surfactants are non-ionic, anionic, cationic, and Witter ionic surfactants. This impacts ionic surfactants. As a result, they are vulnerable to stability concerns

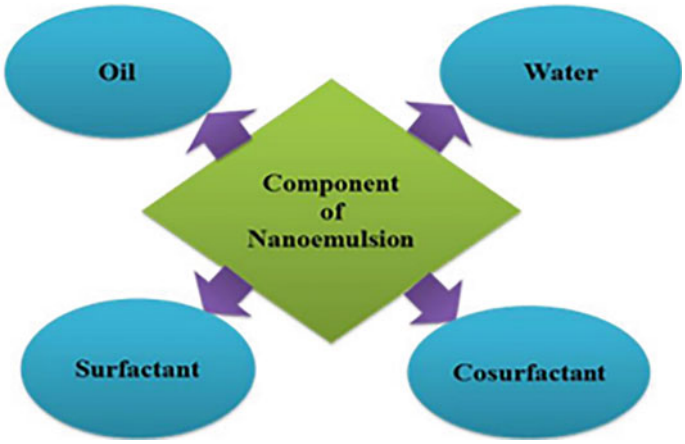

Fig. 4 Nano-emulsion components [29]

and typically are not favored because of toxicity worries. However, non-ionic surfactants are more common than other types because they may be used to make safe medicinal dosage forms.

The following are examples of non-ionic surfactants:

Co-surfactant: High quantities of single-chain surfactants are needed to lower the interfacial tension between oil and water to the point where a nano-emulsion can spontaneously form. Co-surfactants rise the fluidity of the interface because it contains fluidizing groups such as unsaturated bonds, which destroys the liquid crystal or gel structure and changes the HLB value in a way that results in the spontaneous creation of nano-emulsion.

Aqueous Phase: The aqueous phase's characteristics, such as potential of hydrogen (pH), ionic concentration, and electrolytes, have an impact on the stability and droplet size of the nano-emulsion. For the examination of spontaneous nano-emulsification of nano-emulsion, aqueous phases such as plain water, simulated gastric fluid (pH 1.2), Ringer's solution, simulated intestinal fluid (pH 6.8), and phosphate buffered saline can be utilized. Based on the aqueous phase's aforementioned characteristics, when a medication with pH-dependent solubility is added to the system, the phase behavior of nano-emulsions can be drastically affected. Consider the following illustration to comprehend the makeup of a nano-emulsion. Using the medication mebudipine, *Samira Khan* and colleagues developed and assessed an oral nano-emulsion drug delivery system. In this instance, deionized water served as the aqueous phase, Tween 80 and Span 80 served as surfactants, and ethanol served as a co-surfactant. Emulsion formulations are frequently used to dispense medications because they improve the pharmacokinetic profile, increase the solubility of hydrophobic chemicals, and lessen side effects that patients may encounter [36, 62]. Emulsions can be given to patients in many ways, which are shown in Fig. 5.

4 Manufacturing Nano-Emulsions

As two incompatible phases are forced together mechanically, the scattered phase is sheared into tiny droplets, forming an emulsion. It is possible to distinguish between high and low energy sources of shear force used to create emulsions by employing a device to implement the shear force (high energy) or by comprehending how the physical properties of each liquid phase and the chosen surfactants modify as a result of the chemical or thermal energy in the system (low energy). It takes two steps to create nano-emulsions: coarse emulsions must be developed, and then the large droplets must be broken down into nanoparticles using high-pressure homogenization or ultrasonication. They are prepared using a variety of techniques, including high- and low-energy emulsification techniques and combination techniques. High-energy stirring, ultrasonic emulsification, high-pressure homogenization, microfluidics, and membrane emulsification are prioritized among the high-energy approaches. The

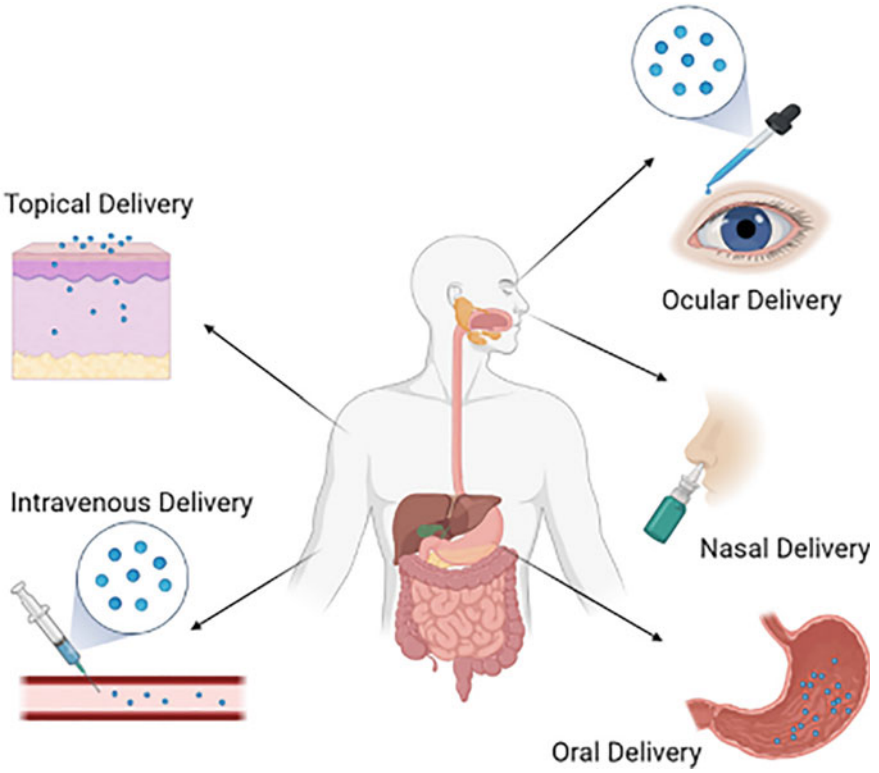

Fig. 5 Various methods of administering drugs delivered via Nano-emulsion [81]

phase inversion temperature method, the emulsion inversion point method, and spontaneous emulsification are the low-energy emulsification techniques that receive the most consideration. Reverse nano-emulsions may be made in dense environments using a combination technique that combines high-energy and low-energy emulsification [44].

4.1 Method of Preparation of Nano-Emulsion

4.1.1 High-Pressure Homogenization (HPH) Method

High pressure is applied to a system consisting of an oil phase, an aqueous phase, and a surfactant or co-surfactant to carry out this operation. With the use of the homogenizer, pressure is exerted. Poor productivity and component degradation owing to excessive heat generation are some issues with homogenizers. This technique can only be used to create liquid O/W nano-emulsions with less than 20% oil phase;

it cannot generate cream nano-emulsions with high viscosities or hardness with a mean droplet diameter smaller than 200 nm. By using this technique, an oil fraction of 20% O/W nano-emulsions may be created. With rising oil content, average droplet diameters increase, as *Anne Desrumaux* and her colleagues demonstrated, because of the constraint on surface-active agents in most oil-concentrated emulsions caused by the significant rise in the interfacial area produced via the homogenizing procedures [65].

Furthermore, the development of droplet clusters or aggregates, which leads to a rise in droplet size, can be blamed for the majority of oil-concentrated emulsions' shear-thinning tendency. Therefore, using the high-pressure homogenization technique to prepare W/O nano-emulsions will not be able to produce nano-sized droplets. Here, a system including an oil phase, an aqueous phase, and a surfactant is put under great pressure. A high-pressure homogenizer, also known as a piston homogenizer, is used to carry out this procedure. The microparticles first enter the valve with a slow velocity. The positive-displacement pump, which produces a consistent flow rate, subsequently produces the pressure. A high-velocity liquid that contains microparticles travels between the valve and the seat. Pressure falls concurrently with an increase in velocity. Finally, the fluid is released as a homogenized nano-emulsion [26].

4.1.2 Ultrasonication

Applying ultrasonic radiation to stir particles in a sample is called sonication. Ultrasonic emulsification mostly happens via two methods. First, applying an acoustic field creates interfacial waves that eventually turn unstable and cause the oil phase to erupt as droplets into the water medium. Second, using low-frequency ultrasound results in acoustic cavitation, which is the production and subsequent collapse of microbubbles caused via a sound wave's pressure variation. High amounts of intensely concentrated turbulence are produced by each bubble collapse (a microscopic-scale implosion) occurrence. The original droplets of dispersed oil are effectively broken up into droplets of sub-micron size using turbulent micro-implosions [34, 80]. There are two primary processes used in ultrasonic emulsification. It is primarily based on the acoustic field, which produces an interfacial wave-forming oil phase that disperses as droplets in the dispersion system. The second process involves ultrasound, which improves acoustic cavitation and causes microbubbles to develop and burst as a consequence of pressure changes brought on by a single sound wave. Similar to this, other types of extremely localized turbulence are produced, eventually leading to micro implosions that ultimately cause the breakup of big droplets into sub-micron-sized ones [35, 79]. Typically, this method uses solid surfaces that vibrate at 29 kHz or higher frequencies to stir a pre-mixed macroemulsion. Devices with focused horns and sharp ends that use ultrasound that create severe shear and cavitation resulting in droplet breaking are used to produce ultrasonic effects. Researchers have discovered that the majority of ultrasonic systems create an inhomogeneous sound field. As a result, recirculating the emulsion through the area of high power is necessary,

and all droplets should encounter the highest shear rate. Obtaining emulsions with homogeneous droplet sizes at diluted concentrations is also attainable by repeatedly doing this sort of recirculation [82, 84].

Additionally, there are specific issues with the procedures since it is possible to cause lipid oxidation, polysaccharide depolymerization, and protein denaturation.

The best approach for creating a nano-emulsion is this one. The droplet size of a typical emulsion or microemulsion is lowered with a sonication process. However, one drawback of this approach is that it can only be used to make small batches of nano-emulsions; it is not appropriate for large batches. An effective screening method for choosing excipients was developed by Sneh Priya et al. to produce the best nano-emulsion formulation. The model medication utilized was quetiapine fumarate. The ultrasonication method employs a probe sonicator to produce nano-emulsions. It is possible to produce desired qualities by adjusting the quantity of oil, surfactants, and secondary surfactants [58].

4.1.3 Microfluidization

It is a patented manufacturing technique that uses a tool called a microfluidizer. This device applies a high-pressure displacement pump (500–20,000 psi) to move materials through a chamber with microchannels. The materials go to an impingement area and become microscopic particles as they flow through the microchannels. An inline homogenizer processes the liquid phases to create a coarse emulsion. The fine nano-emulsion is then produced via passing the coarse emulsion across a microfluidizer. Up until the required particle size is achieved, this process is repeated. The bigger particles are subsequently filtered out of the nano-emulsion using nitrogen [63, 66]. Most often, the microfluidic membrane approach is chosen. The pharmaceutical sector uses it the most frequently to create delicate emulsions. This technique makes use of a microfluidizer, which generates high pressures. High pressure throughout the procedure propels the macroemulsion to the interaction chamber, allowing for nano-emulsions with submicron-sized particles. The process can be repeated numerous times while adjusting the operating pressure to produce uniform nano-emulsions with the desired particle size. It's a trademarked mixing technique. An apparatus called a microfluidizer is used in this technique.

The substance is pushed through the interaction chamber using a high-pressure positive displacement pump (500–20,000 psi) in this system. Microchannels, which are tiny channels, make up this chamber. The product flows onto an impingement region, producing submicron-sized small particles. In this instance, an inline homogenizer is used to blend and treat two solutions (the aqueous phase and the oily phase) to create a coarse emulsion. A microfluidizer is used further to convert the coarse emulsion into a stable nano-emulsion. It has been proven to be more effective than ultrasonography. Still, because of the expense of manufacturing, the risk of equipment contamination, and the need for aseptic processing, this technology is less useful [29, 63].

4.1.4 Phase Inversion Temperature

Chemical energy from phase changes resulting from the emulsification process is used to create fine dispersion. The proper phase transitions are produced by varying the composition at a constant temperature or the composition at a constant temperature. Based on the idea that a surfactant of the type polyoxyethylene (POE) changes in solubility with temperature, the phase inversion temperature (PIT) approach was developed. Due to the polymer chain's drying with increasing temperature, this surfactant develops a lipophilic nature. At low temperatures, the surfactant monolayer displays a sizable positive spontaneous curvature, resulting in the formation of an oil-swollen micellar solution phase [65]. Low energy and spontaneous emulsification are characteristics of the emulsion inversion point (EIP) approach. At a steady temperature, it leads to the gradual dilution of thermodynamically stable liquid crystals or microemulsions with W/O, respectively, to make direct or inverse nano-emulsions that are thermodynamically unstable but kinetically stable [11, [25, 40, 60]. The PIT approach involves raising the temperature of the emulsion system to shift the surfactant's solubilizing pattern from hydrophilic to lipophilic, which results in the formation of bicontinuous microemulsions and emulsion inversion. There are four steps in the procedure (Fig. 6). (a) When the temperature is below the PIT, a macro-emulsion and primarily hydrophilic non-ionic surfactants are present. (b) As the temperature rises, the surfactants progressively turn lipophilic and are dissolved via the oil phase. In case (c), bicontinuous microemulsions occur when the temperature reaches the PIT. (d) Oil and lipophilic surfactant are mixed with water when the temperature is raised above the PIT, and the emulsion is inverted. The system is then rapidly cooled via water dilution, which instantly makes the surfactant hydrophilic and triggers spontaneous and quick migration to the aqueous phase. As a result of this turbulent displacement, nano-emulsions are created [3].

4.1.5 Spontaneous Emulsification

There are three primary phases in this procedure, which are as follows:

Creating a homogenous organic solution with hydrophilic and lipophilic surfactants dissolved in a water-soluble solvent. After that, the water-miscible solvent is eliminated by evaporation under decreased pressure after the organic phase is introduced into the aqueous phase while being stirred magnetically. The quantification of quercetin or methyl quercetin (MQ) included in topical nano-emulsions was verified by Daniel Fasolo et al. using an isocratic liquid chromatography (LC) technique. The nano-emulsions were made utilizing the spontaneous emulsification technique. In this procedure, the water phase is stirred magnetically for 15 min while an organic phase containing elements of the oil core is injected into it. The organic solvent was then eliminated using evaporation at 40–45 °C under decreased pressure [10, 11, 24].

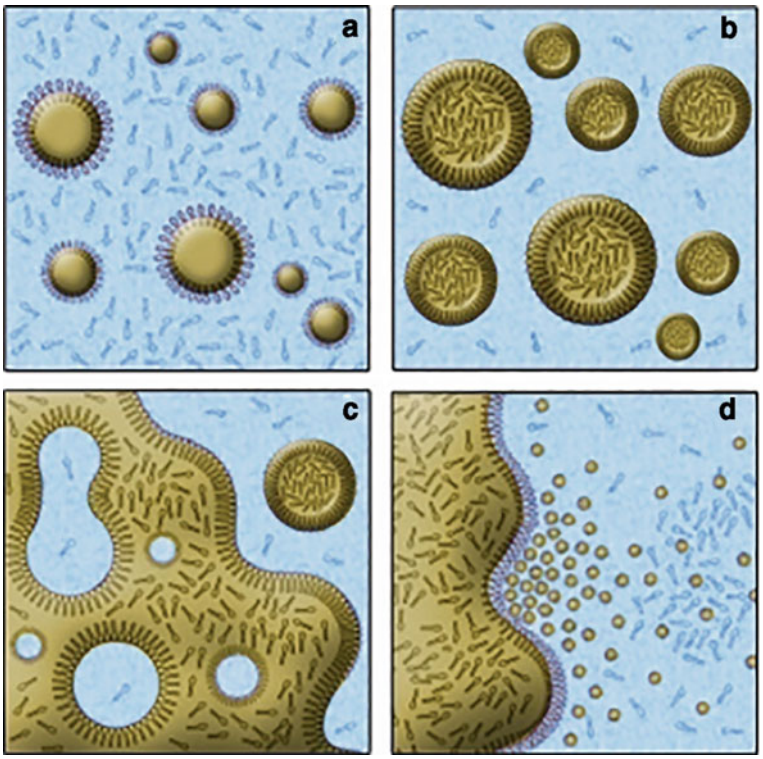

Fig. 6 Making nano-emulsions with the PIT technique. A phase inversion occurs in an oil/water/non-ionic surfactant system [3]

4.1.6 Membrane Emulsification

A low-energy nano-emulsion approach is membrane emulsification. This approach produces an emulsion with a limited size distribution range and requires very little surfactant. This method involves converting a dispersed phase into a continuous phase by passing it through a membrane. This method's disadvantage is that it possesses a negligible dispersed phase flux across the membrane, which can be problematic when scaling up [29].

4.1.7 Emulsion Inversion Point

This method involves varying the system's composition while maintaining a constant temperature. To make the kinetically stable nano-emulsions, dilution with oil or water is done gradually to generate structures [29].

5 Drug Delivery Applications

Nano-emulsions are a new drug delivery technology that enables the regulated or sustained release of genetic material, drugs, and active biological ingredients. Emulsions and surfactants offer a versatile framework for developing various nanomedicines due to the simple manufacture and well-understood characteristics. Because of their small size, they can prolong blood circulation, penetrate deeply into tissues, and engage in special bio-nano interactions. While various hydrophobic cargo, including medicines, photosensitizers, and contrast agents, can be transported in the oil core. Although there has been an increase in interest in nano-emulsions over the past two decades, mainly for the creation of nanoparticles, direct uses of nano-emulsions in consumer items have just recently emerged, primarily in medicine and cosmetics. However, as a result of instability or low solubility in the carrier, medication effectiveness may be severely constrained, so developing effective drug formulations has long been challenging. Nano-emulsion is used to increase the solubility and bioavailability of medications that are not water soluble. The transport characteristics of the drug would be impacted by the nano-sized droplets that would significantly increase the interfacial areas associated with nano-emulsion. This formulation has recently attracted a lot of attention for delivering hydrophilic and hydrophobic pharmaceuticals as drug carriers because of its enhanced ability to solubilize medications, prolonged shelf life, simplicity of production, and increased bioavailability of drugs [41, 72].

5.1 Oral Delivery

The oral route is the most practical, straightforward, and economical method for the non-invasive administration of drugs, thus Based on this concept, medication delivery technologies today control the pharmaceutical industry. Additionally, it is the optimal strategy for achieving treatment objectives due to improved patient comfort. Concerning elderly, pediatric, and maybe trauma epileptic patients, this distribution method has several disadvantages. In addition, due to their nonconducive physiochemical characteristics, certain medications are intrinsically challenging to administer via the oral route. In terms of a drug's gastrointestinal tract (GIT) solubility, stability, and absorption, oral delivery of insoluble medications presents some significant challenges. Peptide medications experience hydrolysis and enzymatic degradation, which restricts their bioactivity and intestinal absorption [47]. Additional downsides might result from some medications' inability to penetrate the cell walls of the epithelium. Using aqueous-dispersible particle delivery methods, solid dispersions, complexing with cyclodextrins, amorphization, and micronization/nanonization are

just a few of the methods that have been proposed to boost the overall drug bioavailability. In the last ten years, numerous research teams using nano-emulsion technology have reported significant increases in the oral bioavailability of hydrophobic and poorly soluble drugs [30, 56].

5.2 Parenteral Delivery

Although drugs with poor solubility are typically thought to be unsuitable for parenteral administration, they are capable of being made into parenteral dosage forms thanks to nano-emulsification techniques. Using biodegradable surfactants guarantees effective pharmacological action without interfering with the body's normal biological processes. According to a recent study, the broadly applied anticonvulsant carbamazepine, which has low solubility, can be made into a nano-emulsion using a spontaneous emulsification process with 2 mg/mL, where 95% of the drug is released in just 11 h. Another study demonstrates that the IV preparation of thalidomide (0.01–0.05% w/w) released 95% of the drug within 4 h of spontaneous emulsification [5, 33]. For this kind of delivery system, choosing the suitable emulsifiers that can create mono- or multilayer structures surrounding the oil droplets to promote the creation of nano-emulsions and increase nano-emulsion stability is crucial. The phospholipids most frequently utilized in the design of parenteral administration systems are semi-synthetic materials, such as di-oleoyl phosphatidylethanolamine (DOPE) and di-stearoyl phosphatidylcholine (DSPC), come from natural sources, such as lecithins. Lecithins can come from either plant or animal sources, making them biocompatible and degradable. The emulsions' long-term stability depends heavily on the proportion of lecithin phospholipids with charged polar head groups. Electrostatic repulsion results from the comparatively high-negative charge that these head groups impart to the droplet surfaces. Although natural surfactants are preferred to synthetic surfactants, adjuvant emulsifying compounds have been utilized to boost emulsion stability since they produce enough emulsification outcomes. Their application is, however, constrained by hemolytic reactions and modifications in the droplet diameter of nano-emulsions stabilized by Tween 80 after autoclaving [67].

5.3 Transdermal and Topical Delivery

Although numerous types of nano-emulsion have been investigated as drug delivery vehicles, it is highly desirable to expand research into dermal and transdermal drug delivery using engineered nano-emulsion technology to broaden its exceptional applications. Topical drug delivery based on nano-emulsions can significantly get around this obstacle. Drugs often enter the skin through three different pathways: sweat ducts, stratum corneum, and hair follicles. The small nanoparticles easily penetrate the pores in nano-emulsions (Fig. 7).

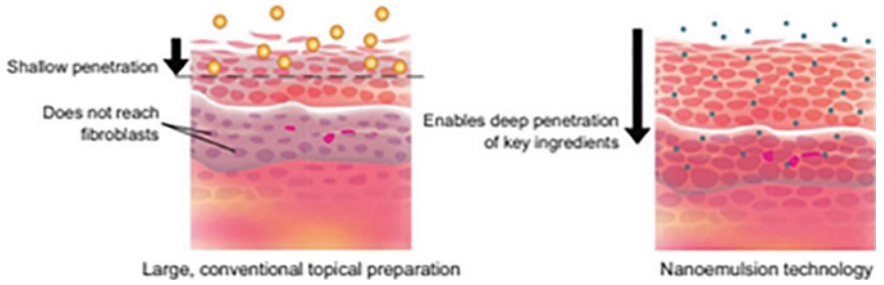

Fig. 7 Comparison of the standard transdermal formulations and nano-emulsions for skin barrier crossing [70]

Although many treatments have been identified, only a few medications have had clinical success. The lower "bioavailability" and poor site specificity are frequently blamed for the lower success rate. The drug administration route, organ physiology, and metabolism primarily influence these measurements [74]. The systemic route shows a rapid fluctuation in drug plasma levels, either below or above, necessitates frequent dosing, and hurts when administered. As a result, systemic medication distribution might occasionally be painful. The skin is the most practical place for medication administration because of its adaptability. It has primarily been used to treat various skin conditions. The transdermal method of medication administration has been regularly used to treat a variety of systemic diseases, including cancer, diabetes, arthritis, and hypertension. It aids in overcoming the limitations of intravenous and oral routes. The molecular size of the drugs and their hydrophilicity or lipophilicity can affect their ability to be delivered topically [22]. Topical medication delivery reduces frequent dosage and helps maintain steady drug plasma levels for longer than oral or parenteral drug administration. The release of medications at the stratum corneum or in deeper layers of the epidermis is ensured by ensuring the interaction of nano-sized globules with skin cells. Because of the smaller droplet size, higher zeta potential, lower polydispersity index, higher elasticity, and a variety of nano-emulsion and emulsifiers, altering the physiochemical properties of drugs enhances their ability to physically interact with cellular membranes and pass through the stratum corneum and epidermal layer [1, 57].

5.4 Intranasal Delivery

Another dependable route for administering some medications is intranasal drug delivery. The nasal mucosa has become a therapeutically effective route for administering systemic medications. Also, it appears helpful to get around barriers to direct drug entry into the target site. Since ancient times, The Indian medical system

Ayurveda has employed this technique. More recently, however, it has gained popularity over oral medication delivery since it promotes greater systemic bioavailability by bypassing the drug's gastrointestinal digestion [48].

Additionally, painless, non-invasive, and well-accepted is the intranasal approach. Targeting medications in the brain presents several challenges, particularly for hydrophilic and high-molecular-weight drugs. This is due to the blood–brain barrier's endothelium's impervious nature, which separates systemic circulation from the brain. The nasal mucosa's olfactory area serves as a direct conduit between the brain and the nose. To treat or manage illnesses, nano-emulsions have been loaded with medications. Polar medicines for treating chronic central nervous system (CNS) disorders like Parkinson's or Alzheimer's disease have been delivered to the CNS by nasal administration. Intranasal administration of vaccines, which is covered elsewhere in this chapter, offers several benefits over oral and parenteral administration. Nevertheless, the main limitations of nasal medication administration are their limited capacity, difficulties in achieving dosage precision, and repeatability. Drug penetration, residence duration, and metabolism in the nasal cavity are frequently influenced by the delivery method, formulation, and administration approach [46, 83].

5.5 Ocular Delivery

Due to its excellent solubility and permeability through barriers, it is one of the most often used ocular drug delivery systems. When made into a nano-emulsion, several poorly soluble medications are now soluble. The typical drug delivery strategy has some limitations, including low bioavailability and a diminished pharmacotherapeutic impact because of subsequent lacrimal discharges from the eye. As demonstrated in Fig. 8, most of the medicine supplied is drained away, resulting in a diminished therapeutic impact. The nano-emulsion is prioritized as one of the therapeutic administration methods because it lengthens the time the medication is in touch with the eye, which solves patient issues including needing to administer drugs frequently. Many research scientists have learned how to create nano-emulsions using high- and low-energy techniques [15, 17].

High-energy methods include ultrasonication, high-shear stirring, and other processes involving the input of high energy and the creation of nanodroplets. Low-energy approaches employ internal chemical changes or temperature changes that result in the production of nanoparticles rather than any external pressure. The phase inversion temperature approach and phase inversion composition technique are two examples.

Because of lacrimal secretion and nasolacrimal drainage in the eyes, conventional eye drops used for ophthalmic medication delivery have low bioavailability and pharmacological effects. Cationic nano-emulsions interact with the negatively charged corneal cells and enhance medication absorption, making them superior delivery systems for ophthalmic drugs (Fig. 9). In a study, dorzolamide hydrochloride, a

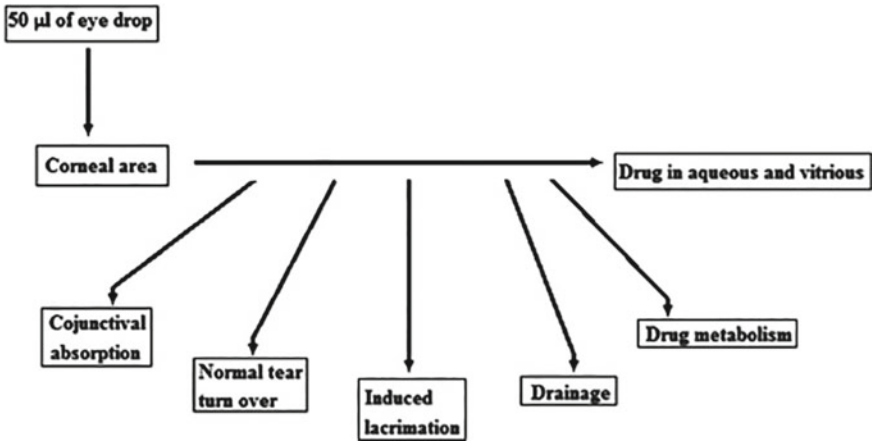

Fig. 8 Challenges to corneal adsorption [17]

possible antiglaucoma medication, was created as an eye nano-emulsion and shown significant therapeutic efficacy and sustained effect [2, 39].

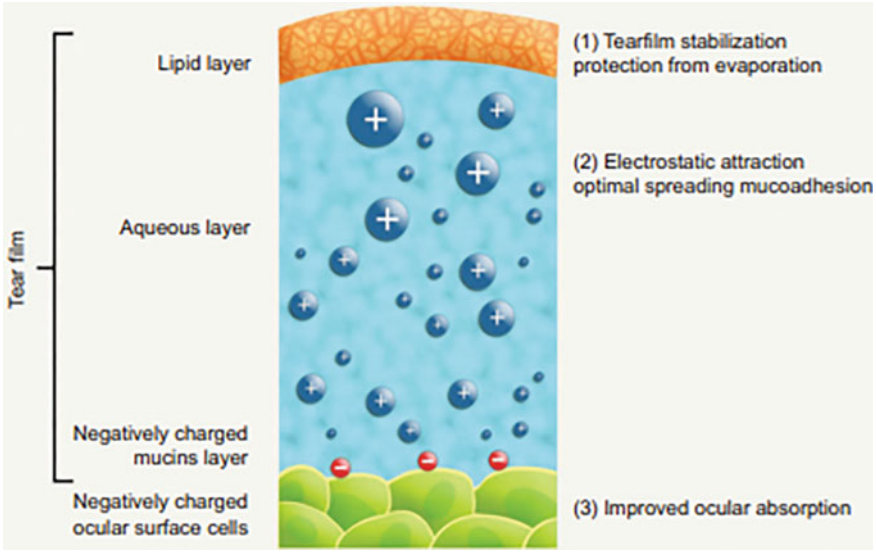

Fig. 9 Cationic nano-emulsions benefits for ophthalmic delivery [39]

6 Kinetics of Drug Release

The foundation of the nanocarrier concept is the notion that extremely tiny nanoparticles can cross biological barriers. The targeted medications are contained by nanocarriers, which can be polymers, amphiphilic lipids, or solid colloidal particles. Gold, ceramic (70), and solid lipid nanoparticles, nanocomposite (71), carbon nanotubes, liposomes, and polymer-drug conjugates are a few types of nanocarriers. The process of encapsulating pharmaceuticals in nanoparticles can be done in several different ways. Nanocarriers are designed to deliver drugs to specific tissues while avoiding the immune system's reaction. One method for making drug-entrapping nanocarriers is to employ a nano-emulsion system. Drugs may either be attached to the surface of nanocarriers or trapped inside them. The nanocarriers are being prepared using a variety of emulsification techniques. The medicine can even be delivered via nanocarriers exceptionally well across the Blood Brain Barrier (BBB) [32, 77].

7 Stability in Nano-Emulsions

Though kinetically stable, there is a chance that the various phases will eventually separate in nano-emulsions. Nano-emulsions are thermodynamically unstable systems that gradually divide into two distinct phases. An effective emulsion can retain its fundamental qualities for weeks or years while having a lengthy shelf life when stabilized by surfactants, making emulsions kinetically stable. This is crucial for translating nano-emulsion into a variety of applications. Still, it's especially essential for emulsion nanomedicine, where gradual formulation changes could negatively impact a patient's health. To ensure that nano-emulsions are prepared and stored correctly, it is crucial to comprehend the processes of emulsion destabilization and stabilization. According to the Derjaguin, Landau, Verwey, and Overbeek (DLVO) hypothesis, attractive van der Waal interactions and repulsive electrostatic double-layer forces combine to provide emulsion stability. Since the two forces are considered separate, adding their sums at certain distances results in the total energy of interaction (FT), which provides a reliable estimate of stability up to around 5 nm. Repulsive forces predominate the contact energy when droplets are far apart, favoring colloid stability. However, when droplets become closer to one another, attractive forces dominate, leading to instability. According to the DLVO hypothesis, the emulsion experiences colloidal instability when the attractive forces take control (Fig. 10) [21, 54].

Larger droplets develop at the expense of smaller droplets during the Ostwald ripening process, which involves the diffusion of the dispersed phase across the continuous phase. The Kelvin effect, which states that particles with a smaller diameter have a higher solubility in solution, causes this process, decreasing the dispersed phase's total surface area and lowering the Gibbs free energy [52]. Ostwald ripening can be prevented by utilizing a dispersed phase with extremely low solubility in

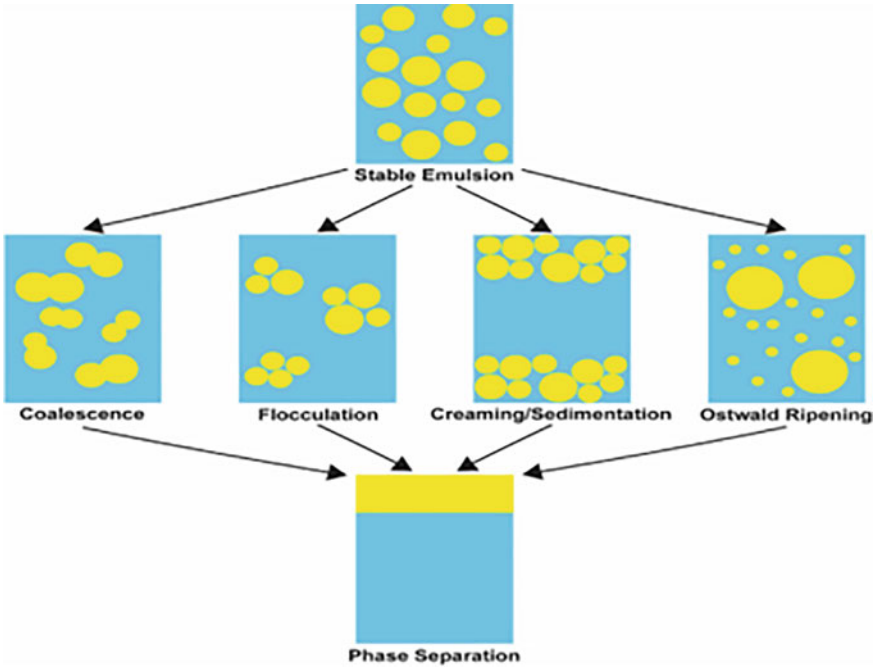

Fig. 10 Emulsion destabilization mechanism illustrated [81]

the continuous phase and making sure that droplet sizes are monodisperse. Ionic surfactant-coated emulsions draw counterions from the solution to create an electrical double layer, which enables electrostatic stability via repulsive forces (Fig. 11) [78]. The Stern layer of tightly bound counter ions, the charged emulsion surface, and a diffuse layer of highly concentrated loosely bound ions and counter ions make up an electrical double layer. The slip plane is where the diffuse layer stops moving together with the emulsion droplets. A crucial indicator of an emulsion's stability is the charge at the slip plane, which is applied to calculate an emulsion's zeta potential and is where particularly positive or negative emulsions are more stable [20].

Droplet size, surface charge, and emulsifier composition directly impact how stable a nano-emulsion is the combined impact of the three factors as mentioned earlier impacts the stability of the nano-emulsion. A good emulsifier mixture creates a flexible interface between two immiscible liquids and aids in suspending the dispersed phase as small droplets in the dispersion medium. Figure 12 provides a typical example. Multi-component biopolymer-based nano-emulsions have been successfully developed using combinations of surfactant, primary electrolyte, and secondary electrolytes [4, 37, 43].

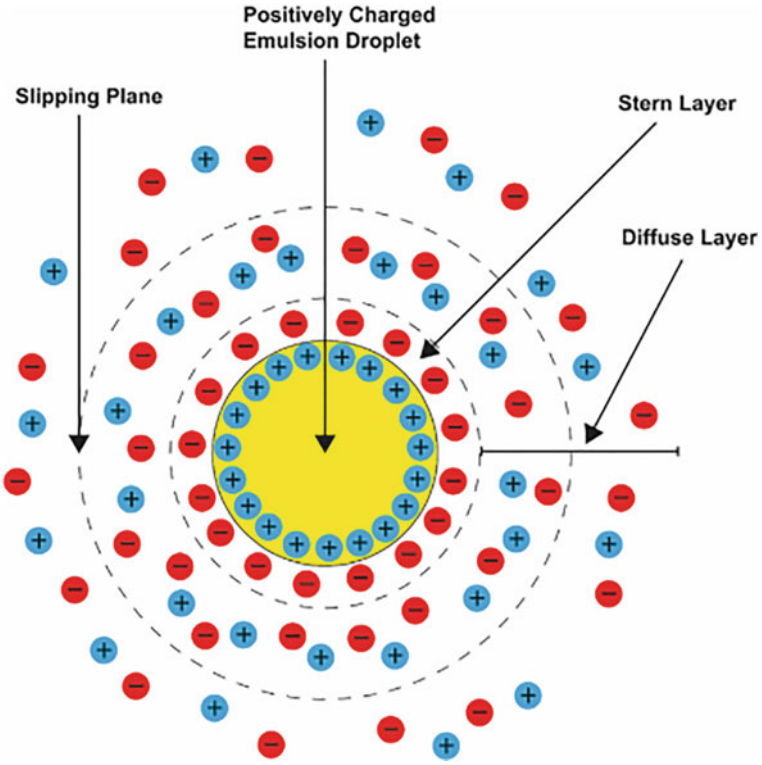

Fig. 11 Illustration of the charged emulsion droplets' electrical double layer [81]

8 Future Prospects

Recently, nano-emulsions have been developed and are currently being tested for various severe diseases and medication therapy-related restrictions. Increases in medication permeability and bioavailability are being made gradually. Recent research by *Mendes* and his colleagues has demonstrated that locoregional injection of lipid nano-emulsion concentrates more in breast cancer while limiting contact with healthy cells. As a result, it could be a potential strategy in neoadjuvant chemotherapy for cancer therapy [50]. *Hyun-Jong Choc* and colleagues discovered that a brand-new lipid nano-emulsion technology might enhance granisetron penetration. Fisetin's nano-emulsion formulation has been shown to increase its bioavailability and anti-tumor efficacy in mice, according to a study team led by Choi et al. [16], Ragelle et al. [59].

Along with nanosuspension and other solubility improvement methods, nano-emulsion has recently emerged as a promising strategy to increase the bioavailability of several medications. Currently, the formulation of several medications as nano-emulsions is being tested.

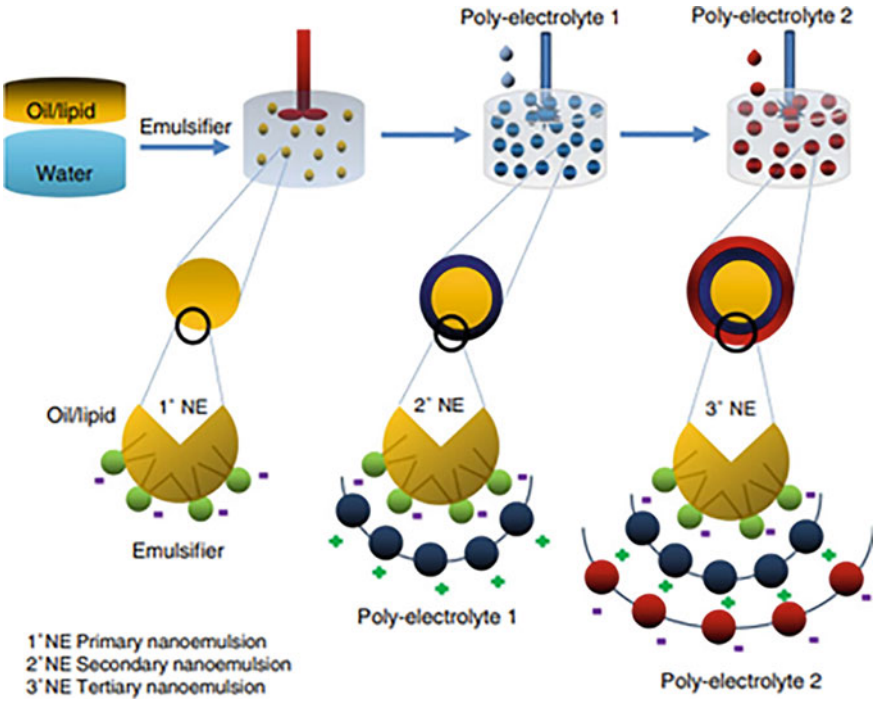

Fig. 12 Stabilization mechanisms [61]

The preparation of nano-emulsions may be done in various ways, giving scientists several options. Nano-emulsification methods are also being used to create nanocarriers, nanoparticles, and nano capsules. The use of nano-emulsions significantly reduces the challenge of piercing physiological membranes. Based on nano emulsification, it is possible to create a variety of medications that would have a considerably lower dosage, be delivered to the intended location, have a higher local concentration, and have fewer adverse effects. Nano-emulsions are erasing barriers to building more specialized and focused medication delivery. As a result, it is emerging as a top formulation choice and has ushered in a new era in the pharmaceutical treatments. In practically all drug administration methods, nano-emulsions are being created and used as pharmaceutical delivery systems. The enhanced solubilization and distribution of poorly soluble actives have received the most outstanding research attention among the many drug delivery applications. To guarantee that this technology is widely used in industry, practical, dependable, safe functional components and cost-efficient, reproducible production techniques are needed [71].

9 Conclusion

Nano-emulsions' ability to solubilize non-polar active chemicals has led to several uses for them as drug delivery methods in the pharmacy field. For the administration of pharmaceuticals, biologicals, or diagnostic agents, nano-emulsion formulations provide some benefits. They can manage drug release, preserve labile pharmaceuticals, improve pharmaceutical solubility, boost bioavailability, and lessen patient variability. Most suggested formulations are self-emulsifying systems due to stability issues, and nano-emulsions are created shortly before use. Although not many applications in other domains have been described, there is a lot of promise for nano-emulsion applications if insoluble oils constrain the Oswald-ripening destabilization process. If breaking and coalescence compete for operations during the process, an optimal shear or temporal shearing may be possible in manufacturing nano-emulsions. Recent work reveals that crossing bicontinuous or continuous aqueous phases during emulsification permits getting O/W nano-emulsions with tiny droplet sizes and low polydispersity. This is relevant to optimization in the creation of nano-emulsions by low-energy techniques. The conclusion is that an ideal surfactant mixture composition or HLB typically exists and that the larger the oil surfactant ratio, the larger the droplet size may be drawn from optimizations by selective adjustment of parameters or experimental designs. If the system is tuned for composition, preparation factors like addition, agitation, or cooling rate often have little to no impact. This conclusion has a crucial derivation: if primary factors have no bearing on the system, it may be scaled up from the lab to the industrial setting with identical outcomes to be anticipated. For over 40 years, clinics have used Nano-emulsions as fluids for whole parenteral feeding. A new path has been made possible by targeting moiety to precisely deliver medications, genes, photosensitizers, and other compounds to the tumor site. As a concluding observation, it appears from the current literature that the preparation and use of nano-emulsions are becoming more popular. It is anticipated that more research will be done in the near future for the clinical implementation of these forms of targeted delivery vehicles.

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