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Review Article

A comprehensive review on applications, preparation & characterization of nanoemulsion

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ABSTRACT

With time, dosage forms have progressed, from essential tablets to advanced systems, which are now more focused on providing better ease of administration to the patients. One such advantageous novel drug delivery system is Nanoemulsion based drug delivery. The Nanoemulsion-based system is reasonably a new means of enhancing drug delivery; Nanoemulsions are sub-micron size particles roughly in the size range of 50-600 nm. The review focuses on conveying information by combining various articles and study reports to understand the work done in this field. This review paper aims to serve as a tool to understand the development of Nanoemulsion. The study comprehensively analyses the preparation methods, composition, characterization, and stability and their application in drug delivery via various routes. Lastly, the paper also describes the recent five formulations prepared for nanoemulsions and their applicability as discussed in the literature.

1. Introduction

This new-fangled era has a lot of improvement in nanoparticle formulation, and as a result, they have applications in a broad range. Currently, numerous categories of nano-preparations are accessible, such as liposomes, polymeric micelle, polymeric Nanoparticles, gold Nanoparticles, and so on. Amongst that, one substantial system is Nanoemulsion. A Nanoemulsion system is a thermodynamically and kinetically stable system.[1,2] The droplet diameter of oil-in-water or water-in-oil Nanoemulsions are ranging from 50 to 100 nm. 100 and 500nm are the standard ranges for droplet size.[3,4] The surfactants that are approved for human consumption are used to form nanoemulsions and FDA-approved food substances that are "generally recognized as safe" (GRAS). Nanoemulsions have the appropriate vehicles even for the parenteral route because of their ability to dissolve the vast number of hydrophobic drugs, as well as their compatibility with one another and capability to prevent the drugs from hydrolysis and enzymatic degradation. The table below represents common differences between two conventional and currently used Nanoemulsion-based systems. The nanoemulsion-based system is an improved version and has better stability compared to the other two systems.[5]

2. Advantages of Nanoemulsions as Drug Delivery Systems

1. Since gravity force is much reduced because of the reduced droplet size, and to rise above gravity Brownian motion is sufficient, during storage creaming and sedimentation cannot be seen.[6] Because of the

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minute droplet size flocculation in droplets is also prevented and enabling the system to remain detached with no division of molecules.
2. Since the surface fluctuations are prohibited, small droplets also avoid their coalescence
3. The competent distribution of active compounds via the skin using nanoemulsions enables quick penetration.
4. The enteric route can be used for nanoemulsions and is formulated with surfactants approved for human consumption (GRAS).
5. Minimized surface tension in the entire system and the minimized interfacial tension of the o/w droplets allow for enhanced wetting, dispersion, and penetration because the small size of the droplet enables them to arrange evenly across the substrate
6. Since nanoemulsions can be formulated as alcohol-free, they can be used in cosmetic products the and scent industry.
7. Because of the lower stability of the Nanoemulsion based system, they may be used as an alternative to liposomes and vesicles.

3. Drawbacks of Nanoemulsion Drug Delivery Systems

1. A large concentration of surfactant and co-surfactant is necessary for stabilizing the nano-droplets.[7,8]
2. The limited capacity of solubility for elevated melting substances.
3. The surfactant ought to be non-hazardous to make it practical for pharmaceutical applications.
4. Nanoemulsion stability is subjective to environmental factors such as temperature and pH.

4. Components of Nanoemulsion

The occurrence of Emulsification is mainly regulated by the features like (1) Oil nature and its concentration, aqueous phase, co-surfactant, and surfactants, (2) The ratio of Surfactant/co-surfactant and Oil/surfactant, (3) Environment's pH and its Temperature and (4) Various physicochemical parameters like lipophilicity, hydrophilicity, and pka-coefficient of the drug.

5. Oil phase

The selection of an appropriate oil phase is critical since it directly regulates the passage of the other elements of nanoemulsions, particularly in the case of o/w nanoemulsions. In general, the oil with the maximum possible solubility with the drug candidate is preferred as an oily phase in the formulation of nanoemulsion. Incorporating both of these criteria into a single oily component is challenging. It is well known that emulsifying oils with extraordinarily long hydrocarbon chains, like soyabean oil, are challenging to emulsify. It is difficult to emulsify the long hydrocarbon chains like medium-chain triglycerides and fatty acid esters. In contrast, the solubilization capacity of lipophilic moieties often increases with oil chain length. The oil phase is typically used as a compromise between the drug's solubilization potential and its contribution to the creation of Nanoemulsions with desired unique properties. To fulfill these requirements oil mixture is used in some cases. For example, medium-chain triglycerides and fixed oils are combined to achieve a better balance between drug loading and emulsification. Recently it has been noted in the literature that medium-chain-momo-and diglycerides-based nanoemulsions have also been identified. For example, medium-chain mono and diglycerides like Capmul ® show better potential in solubilization in comparison to the fixed oils and MCT and are much easier to emulsify. To illustrate Adel F. Alghaith et al 2022, developed a Nanoemulsion loaded with clove oil-naftifine antifungal for the management of tinea. As a result, the formulated Nanoemulsion includes a combination of clove oil and naftifine and shows promising effects for the treatment of tinea.[9]

6. Surfactant

For the formulation of Nanoemulsion, surfactant selection is crucial. Surfactants should promote oily phase Nanoemulsion and have good drug solubilizing capability. It should be mentioned that the surfactants are not innocuous. For example, Tween 20 has good virucidal activity. When choosing a surfactant type and concentration, several parameters must be taken into account. E.g., wherever possible, phospholipids are preferable over synthetic surfactants. MiA minimum concentration of surfactant in Nanoemulsion should be used regardless of the nature, origin, or kind of surfactant. The type of Nanoemulsion would also govern the choice of the surfactant to the formulated.[10,11] Sorbitan monoester, a low HLB surfactant, is favored for w/o Nanoemulsion, while polysorbate 20, a high HLB surfactant, is chosen for o/w Nanoemulsion.[12] To create a Nanoemulsion, it is sometimes necessary to combine lipophilic (low HLB) and hydrophilic (high HLB) surfactants. The numerous kinds of surfactants available for pharmaceutical applications of Nanoemulsion are listed in the table. Among the several surfactants that are offered, lecithin, poloxamer, and polysorbate 20 are the most favored. polyoxyl-40 hydrogenated derivative of castor oil Acrysol® K-150, Acrysol EL135) are utilized in some of the co-solvent-based formulations that are currently marketed.[13,14]

6.1. Co surfactant/Co solvent

Most of the time, surfactant alone cannot lower the oil-water interfacial tension sufficiently to yield a Nanoemulsion which necessitates the addition of an amphiphilic short-

chain molecule or co-surfactant to bring about the surface tension close to zero. The formation of liquid crystalline phases depends on the rigidness of the surfactant film. The solubilization power of the oil is improved by the Co-solvents. Co-solvents like glycerol and propylene glycol are used for Nanoemulsions. Both the co-solvents should be used in high concentration for the Nanoemulsion production, which will result in maximum hydrophilicity. Co-surfactant like PEG 400 can be employed.

6.2. *Aqueous phase*

The aqueous solubility of the oil phase establishes the stability profile of a Nanoemulsion formulation, and proper selection of this base would help to overcome Ostwald ripening. Ostwald ripening is a common disadvantage. The aqueous phase is also significant for the formulation. In the instance of topical Nanoemulsion, distilled water is used as an aqueous phase-in case of parenteral.[15] In nanoemulsion, the aqueous phase should be iso-osmotic to the blood, which can be achieved with the help of additives such as electrolytes (sodium chloride), Glycerol, Dextrose, and Sorbitol. These additives can affect the area of existence of the Nanoemulsions. Electrolytes such as sodium chloride decrease the phase inversion temperature (PIT)of the non-ionic surfactant. Other additives in the aqueous phase such as preservatives, may also affect the Nanoemulsion phase behavior and area of Nanoemulsion existence. Preservatives like methyl paraben and propyl paraben are known to form complexes with surfactants like polysorbate such interactions may influence the properties of Nanoemulsion.

6.3. *Preparation of nanoemulsion*

The drug is to be dissolved in the lipophilic part of the Nanoemulsion. oil and the water phase can be combined with surfactant and a co-surfactant is then added at a slow rate with gradual stirring until the system is transparent. The amount of surfactant and co-surfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of a pseudo-ternary phase diagram. The high-pressure homogenization can finally be used so to achieve the desired size range for dispersed globules it is then being allowed to equilibrate.[16]

6.4. *High-pressure homogenization*

High-pressure homogenizers or piston homogenizers are used in this method to create Nanoemulsions with incredibly small particle sizes (up to 1nm). Nanoemulsions with extremely small droplet sizes are produced as a result of the interaction of numerous factors, including hydraulic shear, severe turbulence, e, and cavitations. Seyed Mehdi Niknam et al. 2022, The authors of this study aimed to create stable water-in-oil systems (W/O) the base used was olive cake extract, and Nanoemulsion was prepared by using mixing and homogenization techniques, The conclusions of the study showed that Stable Nanoemulsion was prepared and had good physical stability.[17]

In the process of producing Nanoemulsions, several techniques can be used to increase the effectiveness of emulsification. Preferably, the Nanoemulsion is prepared at high volume ratios, which may cause coalescence during emulsification, however mor,e surfactant could be used to produce a lesser reduction in effective surface tension and perhaps lessen re-coalescence. Surfactant mixtures with greater surface tension reduction than the individual component could potentially be used. The disperse phase is used for dissolving surfactant rather than the continuous phase, resulting in smaller droplets. It may be beneficial to emulsify in steps of increasing intensity, especially with highly viscous disperse phase emulsions.[18]

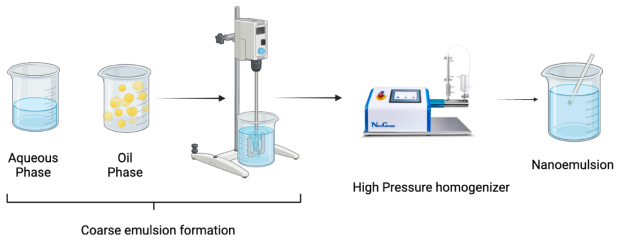

Fig. 1: Nanoemulsion preparation by high-pressure homogenization method

6.5. *Microfluidization*

The Microfluidizer is a device that is used in the patented mixing technique known as “Micro Fluidization”. This device forces the product through the interaction chamber of tiny channels known as “micro-channels” using a high-pressure positive displacement pump (500-20,000 psi). The product passes through the microchannels and onto the impingement area and produced very small particles in the submicron range.

In this method, two solutions (aqueous phase and oily phase) are united together and processed in an in-line homogenizer to create a coarse emulsion which is then allowed into a Microfluidizer where it is further developed to obtain a steady Nanoemulsion. The coarse emulsion is continually passed through an interaction chamber of the MMicrofluidizeruntil the desired particle size is achieved.

To produce a consistent Nanoemulsion, the created emulsion undergoes a filtration procedure under nitrogen that removes the big droplets. Both HHigh-pressure homogenization and micro-fluidization can be used for manufacturing Nanoemulsions for both laboratory scale processes and at the industrial level, while ultrasonic Emulsification is principally used at laboratory scale Micro-fluidization and high-pressure homogenization can both be employed to manufacture nanoemulsion at the

industrial level and the laboratory level, while ultrasonic emulsification is typically used at the laboratory scale.[19]

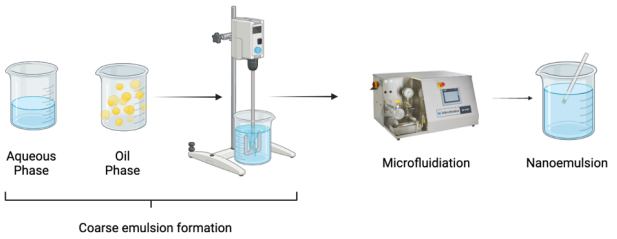

Fig. 2: Nanoemulsion preparation by micro-fluidization method

7. Phase-Inversion Temperature Method

Phase inversion in Emulsions can be one of two types: Transitional inversion induced by changing factors that affect the HLB of the system, e.g., Temperature and Electrolyte Concentration, and Catastrophic inversion, which can also be induced by changing the HLB number of the surfactant at constant temperature using surfactant mixtures. In the PIT method, oil, water, and non-ionic surfactant are mixed at room temperature.[20] This mixture typically comprises o/w micro-emulsions coexisting with excess oil, and the surfactant monolayer exhibits positive curvature. This macro-emulsion is heated gradually, the polyethoxylated surfactant becomes lipophilic, and at higher temperatures, the surfactant gets completely solubilized in the oily phase and the initial o/w emulsion undergoes phase inversion to w/o emulsion. The surfactant monolayer has negative curvature at this stage. This method involves heating the components, and it may be difficult to incorporate thermo labile drugs, such as tretinoin and peptides, without affecting their stability. Although it may be possible to reduce the PIT of the dispersion using a mixture of components (surfactants) with suitable characteristics to minimize degradation of thermo labile drugs.

8. Phase Inversion Composition Method (Self Nano-emulsification Method)

Scientists in several domains, including pharmaceutical sciences, have been very interested in this technology since it produces Nanoemulsion at room temperature without using any organic solvents or heat. Kinetically stable Nanoemulsions with small droplet sizes (50nm) can be created by gradually adding water to a solution of solution in oil with gentle agitation and maintaining a steady temperature. The spontaneous nano-emulsification has been linked to the phase transition during the emulsification process and involves lamellar liquid crystalline phases or bi-continuous micro-emulsion during the process may not be thermodynamically stable, despite having high kinetic energy and long-term colloidal stability.[20]

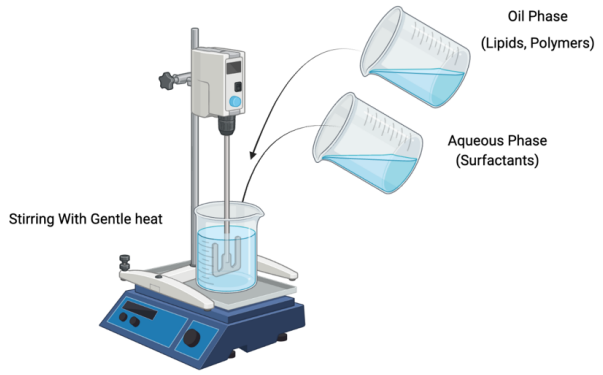

Fig. 3: Nanoemulsion preparation by Phase inversion method (temperature)

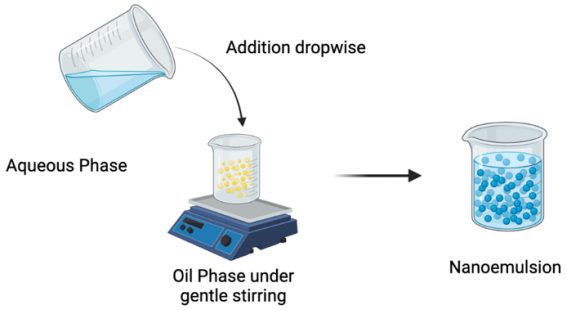

Fig. 4: Nanoemulsion preparation by Phase inversion method (composition)

9. Solvent Displacement Method

The solvent displacement method for the spontaneous fabrication of Nanoemulsion has been adopted from the Nanoprecipitation method used for polymeric nanoparticles. In this method, the oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol, and ethyl methyl ketone. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous Nanoemulsion by rapid diffusion of organic solvent. The organic solvent is removed from the Nanoemulsion by a suitable means, such as vacuum evaporation. The solution of organic solvents containing a small percentage of oil is poured into the aqueous phase without any surfactant. However, the major drawback of this method is the use of organic solvents, such as acetone, which requires additional inputs for their removal from Nanoemulsion. Furthermore, a high ratio of solvent to oil is required to obtain a Nanoemulsion with desirable droplet size. This may be a limiting factor in certain cases of addition; the process of solvent removal may

appear simple at the laboratory scale but can pose several difficulties during scale-up.[21]

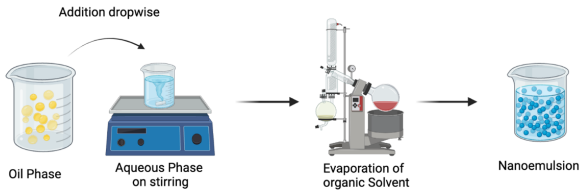

Fig. 5: Nanoemulsion preparation by Solvent displacement method

10. Construction of Pseudo Ternary Phase Diagram

A ternary diagram plot is in chemistry used for depicting chemical compositions. This diagram is three-dimensional but is illustrated in two dimensions for ease of drawing and interpretation. In a ternary diagram, the relative percentage (normally weight %) of three components are represented by A, B, and C. The only requirement is that the three components must sum to 100%. If it's not the case, then one has to normalize them to 100%. A construction of Pseudo-ternary phase-based diagrams of oil, water, and co-surfactant/surfactant mixtures at fixed co-surfactant/surfactant weight ratios. Phase diagrams are being done by mixing the ingredients before which all the ingredients shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. It is subjected to Visual inspection for the confirmation of the formation of mono-phase and bi-phase systems.

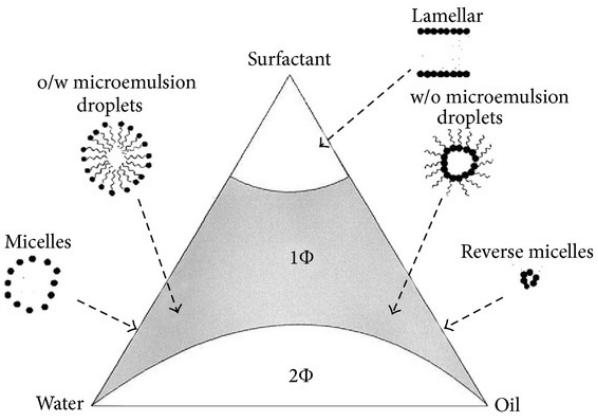

Fig. 6: Ternary phase diagram

If there are signs of turbidity followed by phase separation, the samples shall be notable as biphasic. And if it happens otherwise that is monophasic, clear, and transparent mixture is obtained then they are concluded to be biphasic. If it happens monophasic, clear, and transparent mixtures are visualized after stirring; the sample shall be marked as points in the phase diagram.

11. Applications of Nanoemulsion in Drug Delivery

11.1. Nano-emulsions and intranasal drug delivery

Intranasal drug delivery system has now been recognized as a reliable route for the administration of drugs next to parenteral and oral routes. Nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic drugs and also appears to be a favorable way to overcome the obstacles to the direct entry of drugs to the target site. This route is also Painless, Non-invasive, and well-tolerated. Jursil et. al 2022 recently mentioned in their paper on Blood-Brain Barrier Permeability through Nanoemulsion, in this study the authors explored the possibility of Nanoemulsion crossing the blood-brain barrier, The formulation was prepared using a high-pressure homogenization approach and was characterized for their physicochemical properties. The results of the study show that the optimal composition of VCO-based Nanoemulsion (virgin coconut oil) was recognized as 80% of water (w/v) and 10% of VCO (w/v) that produced a lesser particle size. Not only was it able to cross the Blood Brain Barrier and improve the permeability rate toward the artificial membrane system.[22]

11.2. Nanoemulsions for transdermal drug delivery

Drug delivery through the skin to the systemic circulation is convenient for several clinical conditions due to which there has been considerable interest in this area. It offers the advantage of steady state-controlled drug delivery over an extended time, with self-administration also being possible which may not be the case with the parenteral route. The drug input can be eliminated at any time by the patient just by removing the trans-dermal patch. Their transparent nature and fluidity confer on Nanoemulsion a pleasant skin feel, Nano-sized emulsions can easily penetrate the pores of the skin and reach the systemic circulation thus getting channelized for effective delivery. Nanoemulsion has improved the transdermal permeation of many drugs over conventional topical formulations such as emulsions and gels.[23]

11.3. Nano-emulsions and parenteral drug delivery

Nanoemulsions can dissolve large quantities of hydrophobic drugs, together with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation making nanoemulsions ideal vehicles for parenteral transport. Additionally, the lack of flocculation, sedimentation, and creaming, combined with a large surface area and free energy, offer obvious advantages

over emulsions of larger particle size, for this route of administration. Their very large interfacial area positively influences drug transport and their delivery, along with targeting them to specific sites. Khalil et. al 2015. prepared Nanoemulsion of an anti-tumor drug of benzimidazole derivative. The result of the study shows that physical stability with no phase separation or alteration in particle size was achieved. Chlorambucil, a lipophilic anticancer agent has been used against breast and ovarian cancer. Its pharmacokinetics and anticancer activity have been studied by loading it in parenteral emulsions prepared by a high-energy ultrasonication method. Treatment of colon in Adenocarcinoma in the mouse with this Nanoemulsion leads to a higher tumor suppression rate compared to plain drug solution treatment concluding that the drug-loaded emulsion could be an effective carrier for its delivery in cancer treatment.[24]

11.4. Nanoemulsions and drug targeting

Any formulations, for controlled drug delivery and targeting, Because of their submicron size, can easily be targeted to the tumor area. Although Nanoemulsions are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anti-cancer drugs, Photo-sensitizers, neutron capture therapy agents, or diagnostic agents. The development of magnetic Nanoemulsions is an innovative approach to cancer therapy. In a recent paper by Anas Tarik Alhamdany et. al 2021 in this paper titled Nanoemulsion and Solid Nanoemulsion for Improving Oral Delivery of a Breast Cancer Drug, the authors target oral delivery of Letrozole drug. The constituents were Peppermint oil, tween 80, and transistor P employed as an oil base, surfactant, and co-surfactant. The result of the study signifies that nanoemulsion technology helps in improving the solubility of poorly water-soluble drugs.[25]

11.5. Nanoemulsions and vaccine delivery

A vaccine carrier system using Nanoemulsion is currently being researched. This medication delivery system uses Nanotechnology to vaccinate against human immunodeficiency virus (HIV). There is recent evidence that HIV can infect the mucosal immune system. Consequently, developing mucosal immunity through the use of Nanoemulsions may become very important in the future fight against HIV. The oil-based emulsion is administered in the nose, as opposed to traditional vaccine routes. Research is demonstrating that genital mucosa immunity may be attained with vaccines that are administered into the nasal mucosa.

11.6. Nano-emulsions and pulmonary drug delivery

Emulsion systems have been introduced as alternative gene transfer vectors to liposomes. Other emulsion studies for gene delivery (non-Pulmonary route) have shown that binding of the emulsion/DNA complex was stronger than liposomal carriers. This stable emulsion system delivered genes more efficiently than the liposome. However; extensive studies are required for the successful formulation.[26]

12. Characterization Techniques

12.1. Viscosity

Another quintessential parameter is viscosity. It is determined to understand the rheological properties of the formulation. There are many viscometers employed for the purpose namely, Hoeppler falling ball viscometer, Stormer viscometer, Brookfield visco,m enter, and Ferranti-Shirley viscometer. Among all these Brookfield Rheometer is given a preference. Viscosity measurement can aid to obtain data about the type of emulsion whether it is o/w or w/o, as low viscosity indicated o/w emulsion and the opposite marks w/o emulsion.[27]

12.2. Phase separation test

This parameter is performed to understand the separating behavior of the formulation and hence the same excess quantity of water and oil is added to the formulation which is then visually observed for clarity and separation of the oil phase/water phase. The process is performed 50 to 100 times and the reading is taken in triplicates and the average reading is taken into consideration.

12.3. Centrifugation

This parameter is also performed to check the phase separation or creaming, however here it is done by instrumental means i.e., Centrifuge. The prepared formulation is centrifuged at a speed of 5000-10000 RPM for 10-15 minutes which is then observed visually for creaming of phase separation.

12.4. pH

The final pH of the formulation is to be known before administration as it always affects the route of administration in addition it might change the nature of the formulation from cationic to anionic or anionic to cationic which can directly affect the stability of the overall formulation. The pH is checked with the help of a digital pH meter.

12.5. Stability

The prepared formulation is kept in the stability chamber at different temperature conditions based on the ICH guidelines, both stability and Accelerated stability studies have to be performed to determine the stability of the formulation in different temperature conditions.

The stability can be known firstly by visual appearance, Secondly, the globule size and the charge of the formulation is to be known with the help of a zeta sizer, lastly, drug content is checked by UV-vis spectroscopy and is compared with the drug content of the same formulation before allowing it in the stability chamber.

12.6. Zeta potential

Zeta potential is known by an instrument known as Zeta-Sizer which is used to measure the charge on the surface of the droplets of the Nanoemulsion formulation. The values of Zeta potential lower than-30 mV normally indicate the evasion of physical stability. Mostly Malvern Zeta-sizer is used for this purpose.

13. Atomic Force Microscopy

This new technique of microscopy has been employed recently which explores the surface morphology of the NE formulations. AFM can contribute by providing data in regards to the surface interaction forces at a certain nanometer scale and the imaging of micro/nano-structured surface topography presented under different environmental conditions (air – "dry mode", aqueous – "wet mode", and vacuum).

13.1. Fluorescence test

Several oils turn fluorescent under the presence of UV light while water does not show such behavior.

13.2. Conductivity test

To perform this test current is allowed to pass through the emulsion connected to a voltage bulb, if it lights it is an o/w emulsion as it is commonly known that water tends to be a good conductor of electricity, and when it happens otherwise that is when the bulb does not light up it is w/o emulsion as oil serves to be a non-conductor of electricity.

14. Transmission Electron Microscopy (TEM)

This microscopic technique gives you the data about morphology of the NE formulation. It works on a principle of Combination of bright field imaging which at increasing magnification at diffraction modes divulges the form and size of the Nanoemulsion.

15. Refractive Index

An abbe-type refractometer is to understand the RI of NE formulations. To measure RI a drop of Nanoemulsion formulation is placed on the slide to know the RI it is compared with the Refractive index of water. the If refractive index of Nanoemulsion is equal to that of water, then the prepared formulation of NE is considered to have a transparent nature.

16. In-vitro Studies

It is performed by Keshary Chien-diffusion cell. To achieve this permeation study, the animal used is an adult male rat. First, rats are chosen with a weight of 250±10 g, and the abdominal skin is removed. Then the rat skin is placed between the donor and the receiver chambers of diffusion cells.

37°C temperature has to be maintained in receiver chambers containing fresh water with 20 % ethanol and keep the contents stirring at 300rpm. The formulations are kept in the donor chamber. At specific time intervals such as 2, 4, and 6 hours, a certain amount (0.5 ml) of the solution from the receiver chamber was removed for performing gas chromatographic analysis and each time replaced with an equivalent volume of the fresh solution immediately. Each study is done in triplicates. Cumulative corrections obtained the total amount of drug permeated through rat skins at each time interval and plotted against the time function.[28,29]

17. Future Perspective

Nanoemulsions have achieved attractiveness over the past decade because of their exceptional features such as high surface area, transparent appearance, and stability. As discussed in the article, the most extensively used methods for the preparation of nanoemulsions: are high-pressure homogenization and ultra-sonication, phase inversion temperature, and micro-fluidization. There is a diminutive perceptive on the possibility of industrial applicability, and rational scale-up methods are not studied far and wide. Nano-emulsification system has an excellent perspective for applications in the drug pharmaceutical industry. The nanoemulsion-based delivery systems can advance the product's functionalities and bring superiority and increased shelf life.

18. Source of Funding

None.

19. Conflict of Interest

None.

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