International Journal of Health Care and Nursing (IJHCN)
Volume 2, Issue No. 1, 2023 ISSN Number: 2583-6463
Frequency: Half Yearly Doi: https://doi.org/10.55938/ijhcn.v2i1.43

Review on Nano-Emulsion Drug Delivery System and Formulation, Evaluation and Their Pharmaceutical Applications

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Abstract Nano-emulsion drug delivery system such as develop to eliminate the limitations with traditional drug administration system. This review provided a good overview of the recent advances in the Nano-emulsion drug delivery system. These are nano-sized submicron emulsions developed to enhanced the circulates of active pharmaceutical ingredients to targeted site. Nano-emulsion is a homogeneous mixture of lipid and aqueous phase and stabilization is obtained through the use of an effective substance such as emulsifying agents. The droplet size has been range between the 50-500 nm. The size and shape of the substance distributed throughout the usual process differentiates of emulsion, micro-emulsion, and nano-emulsion. Nano-emulsion gives a novel dosage form for less water solubility drugs and increases pharmacological activity of drugs. Nano-emulsion is used in the future cosmetic industry, diagnostic testing, drug treatment, and biotechnology. This analysis aims to include brief information on the nano-emulsion, advantages, disadvantages, limitations of nano-emulsion, types of nano-emulsion, components of formulations, surface active agents (Surfactant), preparation methods, characterization methods with strong attention of different pharmaceutical applications of nano-emulsion in a different area such as cancer and tumors therapy, targeted drug delivery, mucosal vaccine, trans-dermal drug delivery system.

Keywords

Nano-emulsion, Types of Nano- emulsion, Surfactants, Novel drug delivery, Pharmaceutical Application.

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INTRODUCTION

Nano-emulsions have the capability to be used in the pharmacy sector due to their great opacity at excellent droplet volumetric fractions, increased incidence of migration or bioavailability, and longer biopharmaceutical shelf life.[1] Nano-emulsion is a versatile mode of drug delivery system. This is an unique drug delivery system approach for increasing the bioavailability of drugs that are less soluble in water. The technique of dispersing two incompatible liquids and water—into an isotropic-ally transparent nano-emulsion that is energetically favorable and stabilised by a buffer mechanism. [2] Nano-emulsion is an iso-tropic combination of oils, surfactant system, water, and drugs.[3] These are one of the colloidal particle nanosystems, It contains a droplet size range to acting in a carriers of drug material.[4] Nano-emulsion drug delivery system improves the bioavailability, pharmacological action of the drug, and also reduces the toxic effects of drugs. [5] Nano-emulsion has composed of the concentration ratio of oils and Surfactant system, it contains droplet size 50-500 nm and the structure has been shown in figure 1. [6]

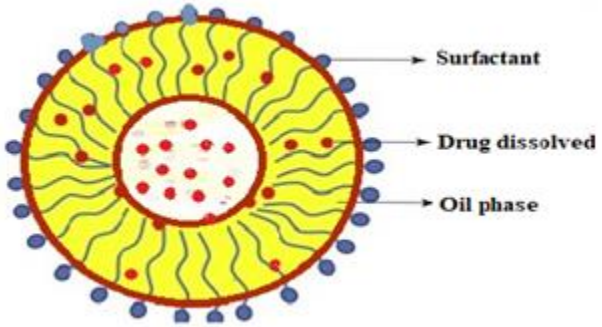

Fig 1: Structure of Nano emulsion

Nano-emulsions are considered transparent stable emulsions composed of two immiscible liquids with particles smaller than 500 nm in size. The formulation of bioactive substances in such nano-emulsions ensures greater bioavailability. [7]

Nano-emulsion has been shown that, with aid of nano-emulsion, the survival time of a drug in the body system could be enhanced such that a low volume of drug is needed for therapeutic

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action. Previous research has shown that nano-emulsion processing can improve the bioavailability of lipid-soluble drugs.[8]

O/ W type of nano-emulsion formulation has been prepared for a long time, but water in the oil type of nano-emulsion has recently been studied by K.L and fester. Both types of nano-emulsion involve different advantages, such as pharmaceuticals and cosmeceuticals.[9] Recently this type of dosage form is frequently used for the delivery of different bio-pharmaceuticals like vaccines, DNA encoded medications and antibiotics. a nano-emulsion drug delivery system is used as a cosmetic and topical preparation.

This system has a great benefit over the other dosage forms in that its formulation can be distributed through different routes, including oral, ocular, and trans-dermal routes. In this article, we try to explain the different aspects involved in the manufacture of nano-emulsion, the form of emulsifying agents, various issues during the style and innovation of the nano-emulsion delivery system According to the extremely tiny teardrop width, ensures stability towards sedimentation and cremation with the formation of Ostwald the key process of nano-emulsion degradation. [10]

Merits [11-13]

1. It can be utilized as a substitution for Lipid/Protein coted medicament and vesicles.
2. Enhances the bio-availability of drugs.
3. Nano-emulsion is a non-toxic and non-irritating.
4. Physical stability has been enhanced.
5. Nano emulsions provide droplets with a wider surface area having increased absorption.
6. Nano-emulsion is developed in many formulations like- foam, cream, oil, and sprays.
7. Improves the solubility of lipophilic drugs.
8. Helpful in masking the odor.
9. There is a need for less energy.

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DISADVANTAGES OF NANO-EMULSION [14-15]

1. Usage of a high Surfactant & co-surfactant ratio required to stabilize nanodroplets.
2. The poor solubilizing ability for fast melting liquids.
   Atmospheric variables like humidity and pH affect on the stability of nanofluids.

LIMITATION OF NANO-EMULSION [16-17]

1. The production of nano-emulsion formulations is a costly procedure, since it is very difficult to minimize size of the droplets, as a particular type of instrument and process system is needed. For eg, the homogenizer (the instrument needed for the formulation of nano emulsions) is a costly operation. Then, micro-fluidification and ultrasound (manufacturing process) demand a large amount of financial help.
2. Nano-emulsion stability is very undesirable and poses a significant issue during the preparation of the formulation for a longer period.

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Table: 1 DIFFERENTIATION OF NANO-EMULSION, MICRO-EMULSION, EMULSION [18-25]

Sr. No.	Parameters	Nano-emulsion	Micro-emulsion	Emulsion
01.	Definition	Iso-tropic combination of gasoline, surfactant system and drug.	Iso-tropic blend of oils, surfactant system, and drug.	The emulsion is a biphasic liquid drug dosage form wherein limited globules can be distributed in another liquid form.
02.	Surface area	High	High	Less
03.	Energy	Very low	Low	High
04.	Droplet size	50-200nm	200-500nm	0.1-10 µ
05.	Appearance	More transparent	Transparent	Cloudy
06.	Formation	Spontaneous formation	Phase titration and phase inversion	Required vigorous shacking
07.	Types	o/w, w/o, bi-continuous	Cylinder,o/w, w/o	w/o/w, o/w, o/w/o,w/o
08.	Viscosity	Very less	Less	More
09.	Stability	Thermo-dynamically and kinetically stable	Thermo-dynamically stable	Thermo-dynamically unstable
10.	Surfactant	Very less	Less	More

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	concentration			
11.	Interfacial tension	Ultra-low	Low	High
12.	Optimization	Pseudo-ternary phase diagram	Ternary phase diagram	Wet gum & dry gum method
13.	Absorption rate	Very fast	Fast	Slow
14.	Bioavailability	Maximum	Intermediate	Minimum
15.	Permeation	Maximum	Intermediate	Minimum

TYPES OF NANO-EMULSION

Nano-emulsions were most generally divided into three types such as O/W or W/O type and bi-continuous type.[26-29]

1. **O/W nano emulsion** Oil in water nano emulsion is obtained naturally by combining two immiscible liquids (water and oil) in the availability of a surfactant. This form of nano-emulsion often has a greater amount of infraction than for the water-in-oil nano-emulsion.[30] In this type, nano emulsion can be a surfactant system film creates an oily phase dispersed in aqueous phase, which is a repeated phase, in a droplet circle. This form of nano emulsion is usually more transient than W/O nano emulsion, [31]and method of preparation of oil in water nano emulsion shows below fig;2.

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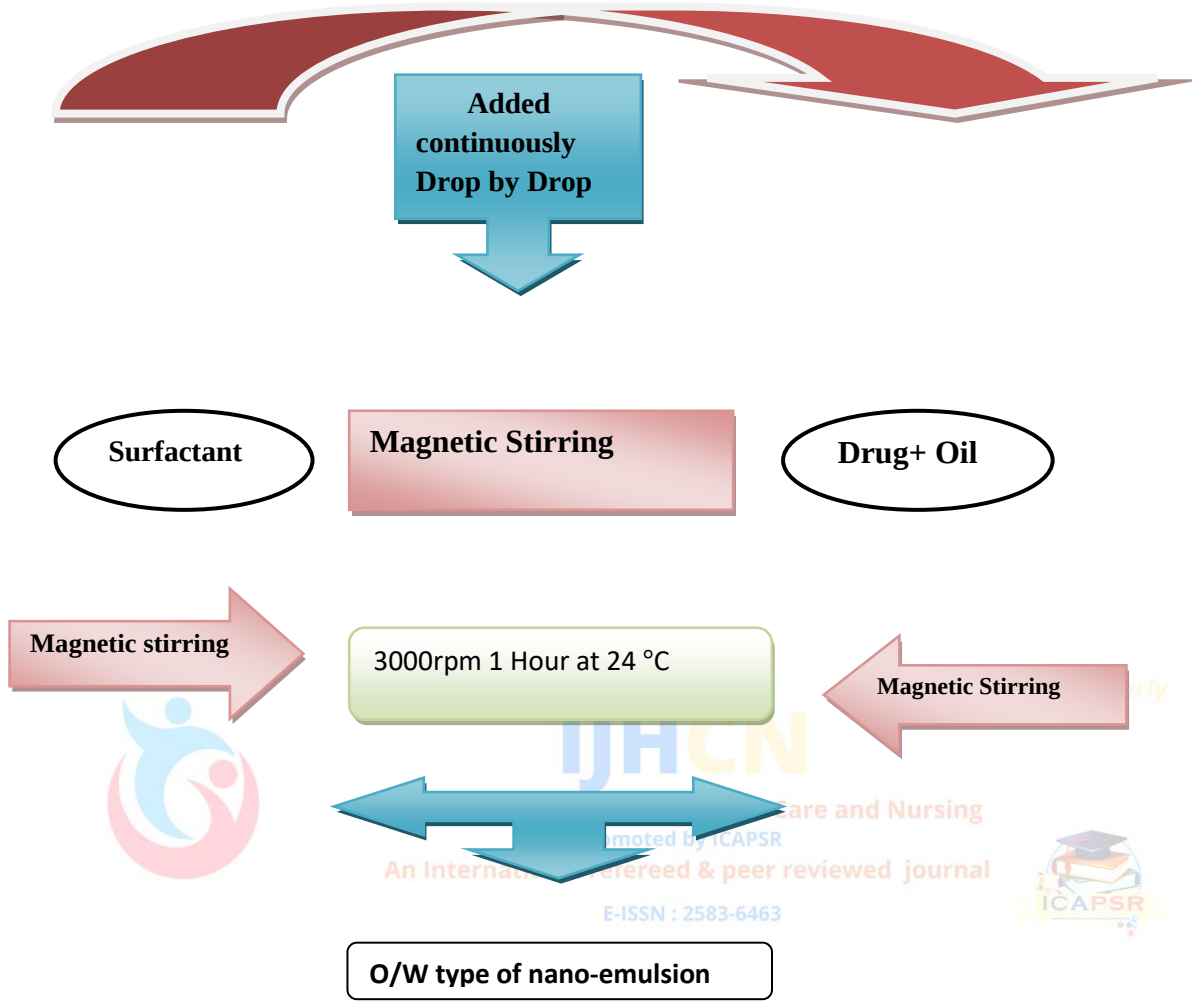

Fig 2- Preparation of Oil/Water Nano-emulsion

W/O nano-emulsion One way to recognise a water-in-oil category nano-emulsion is as tiny particles of liquid encircled by a standard oil phase. These are checked as "revermicelles" where polar head groups of surfactants are found in the oil process with fatty acid tails in water droplets. [32]

Bi-continuous Nano-emulsion Since the process micro-domains of oil and water are interspersed under the system, bi-continuous nano-emulsion may be observed. [33]

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COMPONENTS OF NANO-EMULSION Nano-emulsions with a particle size between 10 and 1,000 nm.[34] As a drug carrier, they improve the clinical effectiveness and reduce toxic effects of the drug. [35] It's a poor thermodynamic approach, but the presence of a surfactant can stabilise it (emulgent or emulsifier). [36] The nano-disseminated emulsion's phase is also referred to as its continuous phase, while its other phase is referred to as its dissolution medium. The micelles are also referred to as intermediary or flexible. [37]

Nano-emulsion contains primarily three components-oil, water, and surfactant. The consistency and properties of the emulsion are determined by the perfect combination of these materials. [38]

The following types of ingredients are used for formulating and developing nano-emulsions. Generally, lipids and surface-active agents are used in nano-emulsion which should be nontoxic, clinically acceptable, biodegradable, and biocompatible.

Oil Phase The selection of the appropriate oily phase is critical because it influences the choice of other nano-emulsion materials, particularly in the case of O/W nano-emulsion. Typically, the oil with the highest emulsifying capacity of the chosen candidate drug is chosen as an oily step for the composition of nano-emulsions, which aids in drug loading in nano-emulsions. [39-42]

Aqueous phase The water phase may contain hydro lover active ingredients and protecting agents. Many times buffer solutions are used as water phase, “water phase also called aqueous phase”. A water sample known as an aqueous layer includes some water-soluble compounds as well as water as one of its main constituents. [43]

Surfactant Surfactants have materials in both water-soluble and lipid-soluble environment in their chemical structure. According to their amphiphilic nature, surfactants make dispersion Bi continuous steps lowering the concerns pertaining to create a flexible film that can expand throughout the particles with the ideal geometry. [44] Surfactants are often classified based on the value of the hydrophilic-lipophilic balance (HLB), an objective number ranging from 0 to 20.

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[45] The electronic conductivity of surfactants has a significant effect on the formation and strength of the composition.

Cationic surfactant

Cationic surfactant is met in an aqueous phase; it produces amphiphilic cation and negative types, the halogen varieties.[46] There are surfactants composed of a head that is positively charged. The surface-active official's cationic nature, which destroys bacterial and viral epithelium, is typically incompatible with the realm of non-ionic and anionic payloads. [47] Alkyl trimethylammonium salts, including cetyltri-methylammonium bromide (CTAB) and cetyltri-methylammonium chloride, are present in ammonium sulfate cations that are constantly energized.[48]

Anionic surfactant

The anionic surfactant arrives with water; It offers a positively (Na, k) or ammonium sulfate cation as well as an amphoteric anion. The anionic surface-active material has anionic molecular orbitals including phosphate, sulphate, carboxylates, and sulfonate at the cap. [49-50]

Non-ionic surfactants

Non-ionic surface-active agents can be stable via interacting with the water is probably hydrophobic interface and hydrate layer via polarity and hydrogen-bonding connections. It is not ionized in water solution and the hydro-lover group is non-separable, being phenol, alcohol, ester, amide, etc.[51] A significant proportion of these nonionic surface-active agents are extracted from hydrophilic from the inclusion of a polyethylene glycol chain**.[52]**

Zwitterionic surfactant

The zwitterionic surfactant can both have Co-surfactants and the binding of both anionic and cationic centres to the same molecule—or both positively and adversely energized groups—can produce nanoparticles. [53-54]

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Co-surfactant Because of the extremely small amount of the covalently link, co-surfactant, which is often a surface-active amphoteric reagent, is unable to stabilise the emulsion properly. However, it is beneficial in the development of nano-emulsion because it therapeutically facilitates the function of the surfactant. [55] In general, the co-surfactant can further decrease the interfacial stress while boosting the hydro-carbons region's responsiveness at the interface, enhancing the vehicle's sturdiness.[56]-

CO-SOLVENTS These are compounds that interact with a combination of two or more different substances that are normally immiscible to make them mixable and which are added to improve the solvent strength of the primary material in a combination often known as a co-solvent. [57] Co-solvents widely used are methanol, ethanol, and water. The potency of a co-solvent is determined by its solubility. That's the highest amount of dissolution of the solute in mixtures of different formulations.

The following factors affect the formulation and development of nano-emulsion drug delivery systems.[58]

1. Selection of the required emulsification system.
2. In order to prevent Oswald from ripening the dispersed process, the basic composition should be extremely insoluble in the dispersed media.
3. To sustain the nano-emulsion drug delivery system, a small amount or concentration of surfactant is required.

Mechanism of Nano-emulsion System Nano-sized mixtures called nano-emulsions were developed to enhance the ingestion of pharmaceutically active ingredients. They'd be stable crystal anisotropy complexes in which an emulsifier, such as a detergent complex like reagent and co-surfactant, is used to emulsify two insoluble liquids to create a particular phase. Nano-emulsions are small-scale emulsions developed to enhance the delivery of therapeutically active ingredients. [59]

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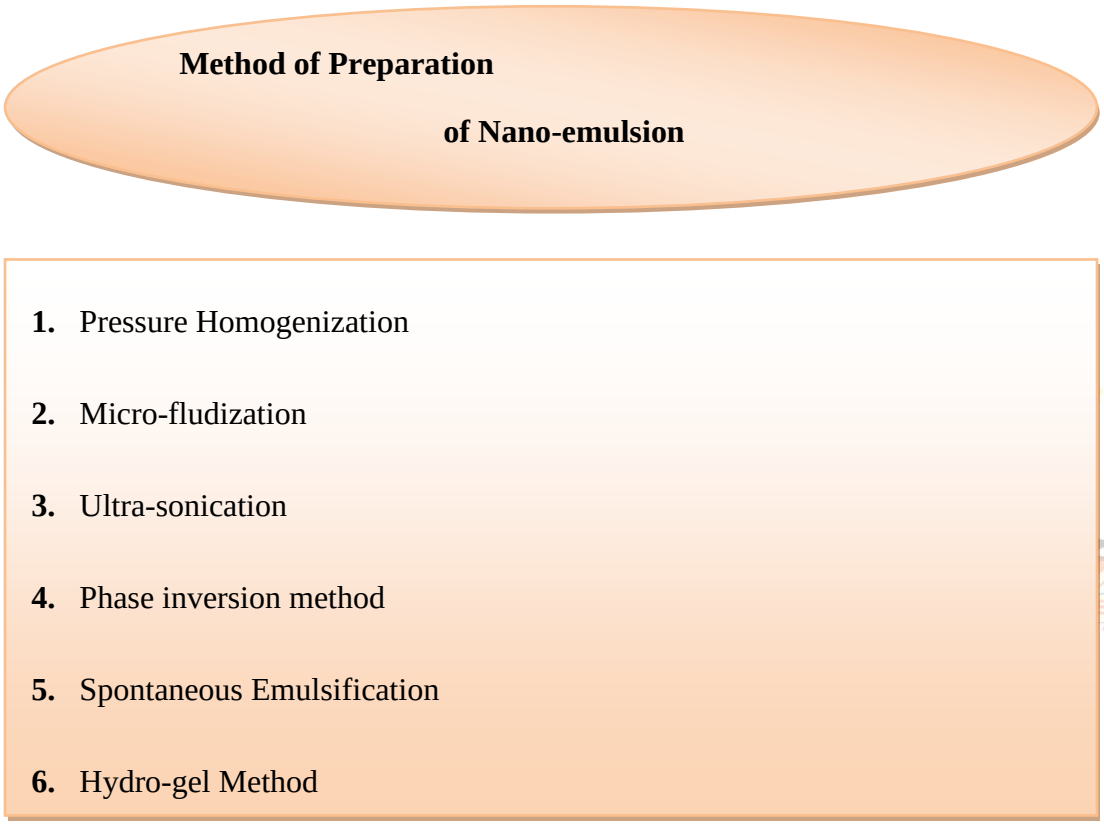
Method of Preparation for Nano-emulsion Drug Delivery System

Nano-emulsions are considered transparent stable emulsions composed of two immiscible liquids with particles smaller than 100 nm in size. [60] The following method of preparation for nano-emulsion drug delivery systems are maintained below; [61-62]



High-Pressure Homogenization

Two liquids (oily phase and water phase) are forced together at extremely high pressure (500–5000 psi) through a tiny input orifice, resulting in extremely thin emulsion particles due to the material's intense friction and kinetic shear. A liquid, lipid-soluble core has been separated from the matching watery core of the particles generated. [63] This method has high quality, the only

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downside is throughout operation, there is a significant increase in emulsion temperatures and resource use. [64]

Micro-fludization Micro-fluidization is a blending technique that uses a device called a micro-fluidified. This system needs a high-pre positive displacement pump (500 to 20000psi) which stresses puts the substance into a space with tiny channels called "micro-channels" for contact. Submicron-sized particles are produced when the material passes past the channel walls and into the area of occlusion. In an internal granulator, the two substances (water phase and oil phase) are combined and removed to produce a coarse emulsion. [65]

Ultrasonication Nano emulsion formulation is recorded in numerous research papers aimed at using ultrasonic sound intensity to minimize the size of a particle. Another solution is the use of a continuous intensity of the sonotrode at device pressures above the atmospheric value. It is well known that rising external pressure raises the Ultrasonic wave cavitation threshold and even less Shape the bubbles. However, there is also a rise in the external influence that increases the strength of cavity bubbles to burst. This indicates that when cavitation happens, the bubble collapsing becomes heavier and more intense than when the strain is in ambient conditions.[65]

Phase inversion method Prospective energies from symmetry breaking created by the flocculating mechanism drives uniform distribution inside this operation. The emulsion's rotation can be changed while maintaining the internal temperature, or vice versa, to produce the transformation. [66]

Spontaneous Emulsification

It involves multiple steps;

i. Formulation of culturally homogenous phase consisting of oils and lipid-soluble surfactant system in a soluble watery solution and a water-soluble surfactant.
ii. The organic layer was infused in the watery medium with in mechanical stir the oil/water emulsion was established.

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iii. The water-soluble solvent has been extracted by convection under decreased pressure.[67]

Solvent Evaporation Technique (SET)

This procedure entails mixing a medication with its emulsifying agent in a different substance that isn't the drug's solvent. Drug precipitates as a result of the solution's vaporisation. By utilising a high-speed stirrer to create significant shear forces, crystallisation may be controlled. [67]

Hydro-gel Method

The sole distinction between these two methods is that the anti-solvent medication makes the solvent ingredient soluble. The growth of crystals and the maturation of Ostwald are both impacted by higher shear strengths.[67]

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Evaluation parameter

Evaluation Parameter

1. Droplet size measurement
2. Viscosity measurement
3. Drug content
4. Refractive index (RI)
5. pH
6. Percentage transmission (PT)
7. Zeta potential Analysis
8. Dilution test
9. Conductivity Test
10. Dye test
11. Uniformity test
12. Thermo-dynamic Stability analysis
13. In Vitro Skin Per-meation Studies
14. In Vivo Pharmaco-dynamics Studies
15. Transmission Electron Microscopy (TEM)
16. Phase Behaviour Study

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Droplet size measurement

Light-scattering analyzer used for measurement particle sizes and a diffusion approach, the particle diameter characterization of a nano-emulsion was assessed. Additionally, it is determined via association spectrometry, which examines the variation in specular reflection brought on by Brownian motion. [68]

Viscosity determination

Viscosity of nano emulsion was analyzed using a rotary viscometer of the Brookfield type at varying shear rate of different temperatures.

Drug content

UV Spectrophoto-metric and HPLC techniques, the formulation quality of the drug content was determined. The 10 mg equivalent of the drug-loaded nano emulsion was dissolved in 100 ml of Solvent, mostly in the UV condition. 10 ml of solvent should be added to 1 ml of this stock solution to dilute it. And the drug concentration was assessed at the drug molecule's recorded Lambda maximum.

pH

The pH of the Nano-emulsion system was measured using a pH metre.

Refractive index

Nano emulsion refractive index was calculated by the Abbe's Refractometer.

Zeta Potential Analysis

The load on the surface of the Nano emulsion droplet was determined by Zeta potential. The formulation (0.1 ml) has been taken diluted 100 times to use double distilled water and measured using Zetasizer.[69]

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Percentage Transmission

Percentage transmission of designed nano-emulsion formulations spectrophotometrically via UV Spectrophotometer at the same Lambda max of a drug molecule.

Conductivity Test

The conductometer system was used for calculated conductivity of the nano emulsion.

Dilution test

The test pertains to the finding that the stability of the nano emulsion was unaffected by the dilution of the continuous step.

Dye test

The colour uniformity of the NE was measured by the Dye test.

Uniformity test

It shows the uniformity of the size of the droplet in the nano emulsion.

Thermodynamic Stability analysis

The designed Nano emulsion has been centrifuge at 1000 RPM for 30 min and examined for the phase separating, cremation. NE having a heating process and six times between the 4°C and 45°C temperatures of the refrigerator were carried out at different temperatures of not less than 48 hours at each temperature. The prepared formulations taken a three freeze thaw cycles between-21°C and +25°C with storing at each temperature not less than 48 hours to verify the thermodynamic stability of nano-emulsion.

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In Vitro Skin Permeation Studies

Using the diffusion method method, improved NE in vitro drug release was evaluated. The dialysis tube contained 1.0 ml of NE, which was discharged into 900 ml of diffusion medium at 100 rpm at 37 0.5°C (pH 6.4 - 6.8 phosphate buffer. Dilutions of 5 mL samples were taken out of the dialyzing medium on a regular basis to maintain the sink condition, and the amount taken out was constantly replenished with fresh medium. With the aid of UV analysis, the sample's partial Lambda max of the drug ingredient was quantified, and the percentage of all controlled release occurrences was calculated. [70]

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) used for morphological and structural analysis of nano emulsion system.

Phase Behaviour Study

The Nano-emulsion system was evaluated using the Pseudo ternary phase diagram. It also defines the field of NE system. [71]

APPLICATION OF NANOEMULSION

Parental Delivery

Nano emulsion has been used in intravenous administration. This path of administration, in specific Necessity only for formation of a droplet scale diameter lower than 1 micrometre. Parental (or Injectable) Nano emulsion administration is used Nutrition for a number of uses, e.g. Fats, carbohydrates, vitamins.[72]

Oral delivery

Nano-emulsion system having a multiple advantages of over traditional formulations for oral delivery, except enhanced absorption, enhanced therapeutic efficacy and reduced drug toxicity.

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Topical delivery

In order to minimize hepatic first-pass metabolism and potential adverse effects, topical delivery of medicines has several advantages over other techniques. The alternative method involves administering the medication directly through the affected area of the skin or eyes.

Ocular delivery

Drugs are used to treat eye disorders mainly delivered topically nano-emulsions Ocular administration, dissolving of poorly soluble drugs, increasing absorption and achieving a prolonged release profile have been investigated.[73]

In cosmetic industry

Aesthetic characteristics, like low viscosity and translucent functional features of nano-emulsion with droplet sizes under 200nm, provide a high surface area that enables the active substance to be easily transferred to the skin, making it highly desirable for use in cosmetics. Nano-emulsion technology to develop a mini-emulsion of oil-in-water concentrate appropriate for reducing transepidermal water loss, improved skin safety and drug penetration.

Nano emulsion in Cancer treatment

In chemotherapeutics, niosomes may be employed as a transporter to prolong the drug's flow after muscular and impact on the surrounding injections (W/O systems). Additionally, since it is a non-irritating approach, it enhances the administration of transdermal medications by improving the lymphatic penetration of anti-cancer therapies via the skin.

Nano emulsions in gene delivery vector

Emulsion systems were devised as prospective liposome genetic manipulation platforms. The retention of the emulsion/DNA pair is stronger than just the encapsulated transmitter, according to other emulsion genetic manipulation experiments (non-pulmonary route). Genes were produced more effectively by this steady emulsion process than by microcapsules. [74]

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Nano-emulsions in nose to brain drug delivery system

A more efficient medicine delivery method than parenteral and oral routes is the noninvasive system of drug administration. Nasal mucosa has developed as a result of medication. Medicines that target the brain are associated with a number of issues, particularly aqueous medications and greater molecular issues. An effective technique to overcome the obstacles preventing the prompt entry of pharmaceuticals into the specific site seems to be an appropriate path for the transport of widespread medications. As a result, the path is non-invasive, painless, and quite well. Due to its low catalase activity and large concentration of completely impervious sites, the mucous membrane is considered one of the most efficient sites. big molar mass molecules. This is because the microvascular, which divides the blood-brain barrier from the circulation, is hermetic in nature. Alzheimer's disease, migraine, epilepsy, schizophrenia, Parkinson's disease, meningitis, etc. can all be treated with stimulant nano-emulsions that target the nostril mucosal olfactory region, which has a direct association between the nostrils as well as the cerebral.[75-76]

CONCLUSION AND DISCUSSION:

Nano-emulsion drug delivery system has been extensively used in pharmaceutical field. Nano-emulsion has been given many advantages of deliver of drug, biochemical. Nano-emulsion was appropriate for multiple route and thus retains a potential for various areas. This technological innovation has solved the issue with few watery soluble drugs and is a tool for insoluble aqueous drugs. Nowadays, nano-emulsion has been used in the selective delivery of different category of the drugs like anti-cancer drugs, photo-sensitizers. Overall, all formulations of nano-emulsion found to be efficient, secure and patient-compliant formulations for pharmaceutical distribution. Further research and progress on nano-emulsion is expected to take place in the future.

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ACKNOWLEDGEMENTS

We thank Dr. Yogendra Bahugana and Dr. Sanjar Alam for generously supporting this work. The authors are highly thankful to **R V Northland Institute, Greater Noida, UP, India** for providing the library facilities for the work.

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