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Review on Design and Evaluation of Herbal Nanoemulsion

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ABSTRACT: Nanoemulsions often have a higher loading capacity for lipophilic active ingredients than microorganisms, which can be advantageous in some applications. The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase, Nanoemulsions often have a higher loading capacity for lipophilic active ingredients than microemulsions, which can be an advantage in some applications. The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase. Herbal medicine is the use of medicinal plants for illness prevention and treatment. It includes everything from traditional and popular remedies from all over the world to standardized and titrated herbal extracts. In herbal medicine, where tradition is almost entirely based on remedies containing active principles at very low and ultra-low concentrations, or relying on magical-energetic principles, general cultural rootedness enduring and widespread use in the traditional Medical System may indicate safety, but not the efficacy of treatment. According to the WHO, 80 % of people worldwide rely on herbal medicines for some part of their basic health care. Polymers are the foundation of a pharmaceutical drug delivery system because they regulate drug release from the device. Polymer is to protect the drug from the physiological environment and prolongs the drug's release in order to improve its stability. In this review, the attention is focused on giving a basic idea about its formulation, method of preparation, characterization techniques, evaluation parameters, and various applications of herbal nanoemulsion. This review gives a detailed idea about an herbal nanoemulsion.

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Keywords: Controlled release drug delivery system (CRDDS), Self Nano emulsifying Drug Delivery (SNEDDS), Polymers, Nanoemulsion, Herbal plants, Patient compliance.

INTRODUCTION:

Herbal medicine is the use of medicinal plants for illness prevention and treatment. It includes everything from traditional and popular remedies from all over the world to standardized and titrated herbal extracts. In herbal medicine, where tradition is almost entirely based on remedies containing active principles at very low and ultra-low concentrations, or relying on magical-energetic principles, general cultural rootedness enduring and widespread use in the traditional Medical System may indicate safety, but not the efficacy of treatment[1]. Herbal

medicine is still the mainstay of about 75 to 80 % of the world population, mainly in developing countries, for primary health care. Plant formulations and mixed extracts of plants are preferred over separate ones in the ancient Indian medical system [1,2].

Difference between Herbal and Conventional Drugs:

Although superficially similar, herbal medicine and conventional pharmacotherapy have three important differences: Use of Whole Plants - Herbalists generally use unpurified plant extracts containing several different constituents. It is claimed that these can work together synergistically so that the effect of the whole herb is greater than the summed effects of its components. It is also claimed that toxicity is reduced when whole herbs are used instead of isolated active ingredients. Although two samples of a particular herbal drug may contain constituent compounds in different proportions, practitioners claim that this does not generally cause clinical problems. There is some experimental evidence for synergy and buffering in certain whole plant preparations, but how far this is applicable to all herbal products is not. Herb Combining- Often several different herbs are used together. Practitioners say that the principles of synergy and buffering apply to combinations of plants and claim that combining herbs improves efficacy and reduces adverse effects. This contrasts with conventional practice, where polypharmacy is generally avoided whenever possible. Diagnosis- Herbal practitioners use different diagnostic principles from conventional practitioners. For example, when treating arthritis, they might observe, the under-functioning of a patient's symptoms of elimination" and decide that the arthritis results from "an accumulation of metabolic waste products. A diuretic, choleretic, or laxative combination of herbs might then be prescribed alongside herbs with anti-inflammatory properties [3].

Use of herbal Medicine:

The earliest evidence of human's use of plants for healing dates back to the Neanderthal period [4]. Herbal medicine is now being used by an increasing number of patients who typically do not report their clinician's concomitant use [5].

Regulation of Herbal Medicine

Herbal remedies for a potpourri range from plants that people collect themselves and then take for health reasons to approved medical products. Many herbal products fall between the far ends of this regulatory range: unlicensed preparations are thought to account for over 80 % of herbal sales. European Union legislation requires herbal products to be authorized for marketing if they are industrially produced and if their presentation of their function, or both, bring them inside its definition of a medicinal product. Unfortunately, drawing a sharp borderline is difficult. Many medicine-like products on the British herbal market remain unregistered for two reasons: acceptable data on efficacy, safety, and quality may not be available, and the licensing fee is high [6].

Safety issue of Herbal Medicines:

Traditional herbal products are heterogeneous in nature. They impose a number of challenges to qualify control, quality assurance, and the regulatory process. Most herbal products on the market today have not been subjected to drug approval processes to demonstrate their safety and effectiveness. Some of them contain mercury, lead, arsenic and corticosteroid, and poisonous organic substances in harmful amounts. Hepatic failure and even death following ingestion of herbal medicine have been reported [7].

Need for Clinical Trials:

To gain public trust and to bring herbal products into the mainstream of today's healthcare system, researchers, manufacturers, and regulatory agencies must apply rigorous scientific methodologies and clinical trials to ensure the quality and consistency of traditional herbal products. Using modern technologies, the quality and consistency of heterogeneous herbal products can be monitored. A well-designed clinical trial is the method of choice to prove the safety and effectiveness of a therapeutic product. Manufacturers of herbal products must adhere to the requirements of good manufacturing practices (GMPs) and preclinical testing before these products can be tested on humans. The basic principles and design of the clinical trials for herbal products are the same as those for single-component chemical products. A number of randomized double-blinded controlled studies have been carried out using herbal formulations. These studies have proven the effectiveness of the herbal products tested and shown few side effects. Thousands of years of traditional use can provide us with valuable guidelines for the selection, preparation, and application of herbal formulations. To be accepted as a viable alternative to Western medicine, the same rigorous methods of scientific and clinical validations must be applied [8].

Bioavailability of Herbal Drugs

The bioavailability of the active constituents of the herb is another area of considerable importance. Before a compound can act systemically it must pass from the gastrointestinal tract into the bloodstream. This is an area in which surprisingly little is known about herbal constituents. Compounds, such as berberine and hydrastine in the popular botanical goldenseal (*Hydrastis canadensis* L.) Are essentially not absorbed following oral consumption. Studies show systemic remains one of the best-selling herbs, is widely promoted, and is accepted by a misinformed public as a nonspecific immune stimulant [9]. The widespread use of herbal medicine is not restricted to developing countries, as it has been estimated that 70 % of all medical doctors in France and Germany regularly prescribe herbal medicine [10]. The number of patients seeking herbal approaches for therapy is also growing exponentially [11]. with the US Food & Drug Administration (FDA) relaxing guidelines for the sake of herbal supplements, the market booming with herbal products [12,13].

The Indian herbal drug market is about $ one billion and the export of herbal crude extract is about $ 80 million.

The widespread use of herbal medicine is not restricted to developing countries. The rebirth of herbal medicine, especially in developed countries, is largely based on a renewed interest by the public and scientific information concerning plants. Herbal remedies are popular among patients with chronic diseases or they are safe, effective, and pure and patient compliance [14]. Nanoemulsion is a Novel drug delivery system. It is one of the novel approaches of drug delivery systems to enhance the Bioavailability of poorly water-soluble drugs. It is an Isotropic mixture of Oil, Surfactant: Cosurfactant (Smix), water, and drug [15]. This Self Nano emulsifying Drug Delivery (SNEDDS) Platform has the unique ability to shape tiny oil-in-water (O/W) nano-emulsions using gentle stirring and a fluid medium. It is just an anisotropy mix of distinctive oils, surfactants, and co-surfactants [16]. Nanoemulsions consist of very fine oil-in-water dispersions, having droplet diameters smaller than 100 nm. Nanoemulsions are very fragile systems by nature. As they are transparent, the slightest sign of destabilization appears visually. Two major sources of instability were identified and extensively studied: Ostwald ripening and depletion-induced flocculation following the addition of thickening polymers. Nanoemulsions are nontoxic and nonirritant systems that can be used for skin or mucous membranes, parenteral and non-parenteral administration in general, and have been utilized in the cosmetic field. Transdermal delivery using nanoemulsions has decreased due to stability problems inherent to this dosage form. Some examples of drugs using nanoemulsions for transdermal drug delivery are gamma-tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin, and nimesulide [17]. Nano Specificity of drug action is a fundamental drawback of traditional oral drug delivery systems due to poor drug formulation. Therefore, it is essential to create drugs with enhanced target specificity that can be accomplished by modifying the pharmacokinetics and pharmacodynamics of the pharmaceuticals used. Nanoemulsions are colloidal particulate systems in the submicron size range acting as carriers of drug molecules. Their size varies from 10 to 1,000 nm. These carriers are solid spheres and their surface is amorphous and lipophilic with a negative charge. Magnetic nanoparticles can be used to enhance site specificity. An emulsion is a biphasic system in which one phase is intimately dispersed in the other phase in the form of minute droplets ranging in diameter from 0.1 to 100 µm. It is a thermodynamically unstable system, which can be stabilized by the presence of an emulsifying agent (emulgent or emulsifier). The dispersed phase is also known as the internal phase or the discontinuous phase while the outer phase is called the dispersion medium, external phase, or continuous phase.

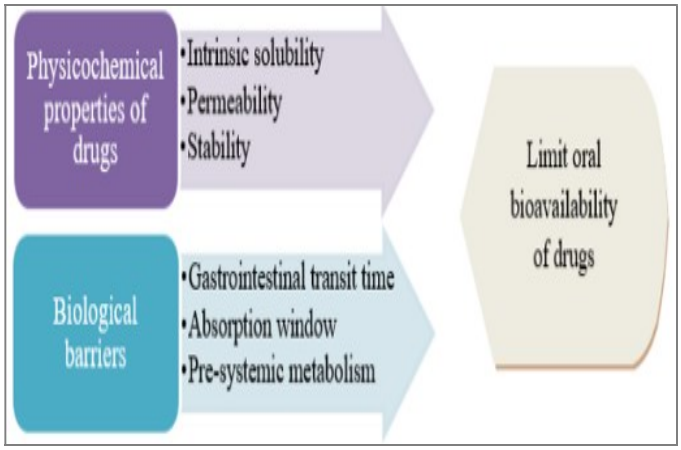

Fig 1. Schematic representation of various challenges to the oral delivery of drugs.

The emulsifying agent is also known as intermediate or interphase. The term 'nano-emulsion' also refers to a mini emulsion which is fine oil/ water or water/oil dispersion stabilized by an interfacial film of surfactant molecules having a droplet size range of 20 to 600 nm. Because of their small size, nanoemulsions are transparent [18].

In the context of human in pharmaceutical, drugs can be classified into four BCS categories:

Class I: High solubility, high permeability- Substance those that are mostly well absorption.

Class II: Low solubility, high permeability- exhibited dissolution rate-limited absorption.

Class III: High solubility, low permeability- exhibited permeability-limited absorption.

Class IV: Low solubility, low permeability- poor oral bioavailability.

BCS drugs are scientifically classified on two factors that are water solubility and Intestinal permeability.

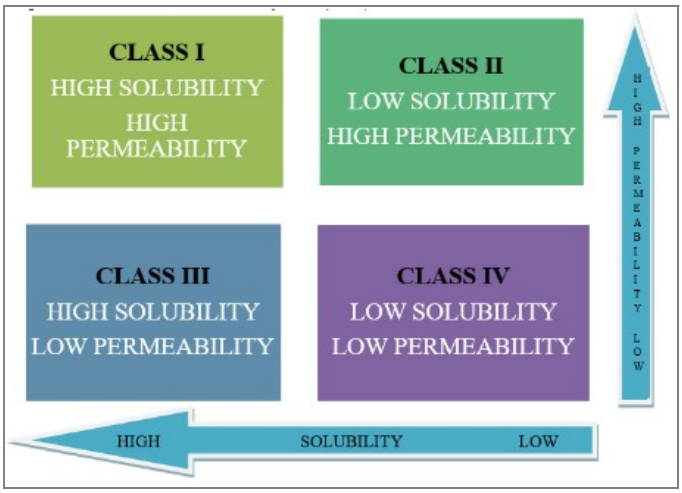

Fig 2. Biopharmaceutical classification system.

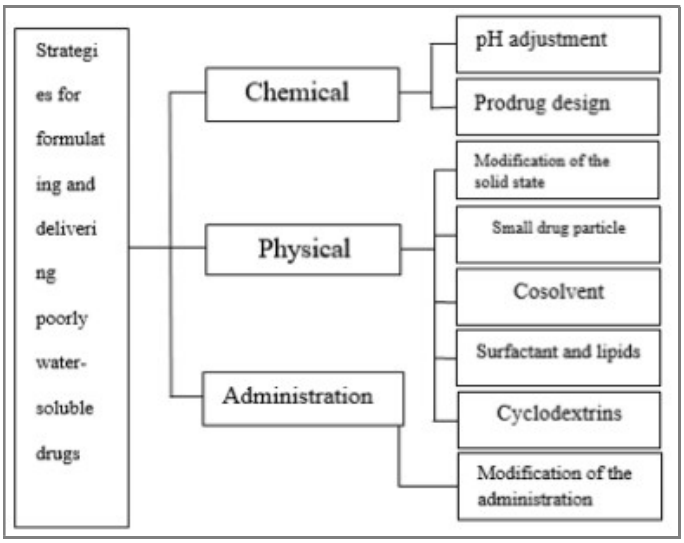

Fig 3. Techniques employed for solubility enhancement of drugs.

NANOEMULSIONS:

Nanoemulsions are novel drug delivery systems consisting of emulsified oil and water systems with an average droplet size of 10 to 200 nm introduction [18].

There are three types of nanoemulsion that can be formed Oil in water nanoemulsion in which oil is dispersed in the continuous aqueous phase; Water in oil nanoemulsion in which water droplets are dispersed in the continuous oil phase; and Bi-continuous nanoemulsion [19].

Advantages of nanoemulsion:

It may be used as a substitute for liposomes. It improves the bioavailability of drugs. It is non - toxic and non-irritant in nature. It has improved physical stability. Nanoemulsion has small-sized droplets having greater surface area providing greater absorption [20,21]. It is thermodynamically stable, optically clear, and transparent. The Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases, a co-surfactant or co-solvent is used in addition to the surfactant [22]. Nowadays nanoemulsions are frequently used for various purposes like delivery of vaccines, DNA-encoded drugs, antibiotics, and cosmetic and topical preparations and can be administered via various routes like oral, pulmonary, ocular, and transdermal [23].

Disadvantages of the Nanoemulsion (NE) System:

The nanoemulsion has a limited solubilizing capacity for high-melting substances [24]. A large concentration of surfactant and co-surfactant is necessary for stabilizing the Nanodroplets [25]. The nanoemulsion stability is influenced by environmental parameters such as temperature and pH [26]. The surfactant should be nontoxic for using pharmaceutical applications.

The formulation of nanoemulsion is an expensive process due to the size reduction of droplets and is very difficult as it requires special kinds of instruments and process methods [27].

Table 1. Difference between Nanoemulsions and emulsions.

Emulsion	Non-emulsion
Unstable	Thermodynamically and kinetically stable.
Cloudy	clear and translucent
Emulsion requires the large energy input	formed either with or without high energy input
20 to 25 % surfactant is added in emulsion preparation	5 to 10 % surfactant is added in Nanoemulsion
smaller surface area to volume	Larger surface area to volume
Less expensive	More Expensive

FORMULATION ADDITIVES FOR NANOEMULSION:

Oils:

Castor oil, coconut oil, corn oil, cottonseed oil, evening primrose oil, fish oil, jojoba oil, lard oil, linseed oil, mineral oil, olive oil, peanut oil, PEG-vegetable oil, perfluorochemicals, pine nut oil, safflower oil, sesame oil, soybean oil, squalene, sunflower oil, wheatgerm oil [28].

Emulsifiers:

Natural lecithins from plant or animal sources, phospholipids, PEG-phospholipids, poloxamers (eg. F68), polysorbates, derivatives, polyglycolized glycerides, stearylamine, oleylamine, polyoxyethylene castor oil.

Antioxidants: α-tocopherol, ascorbic acid.

Tonicity modifiers: Glycerol, sorbitol, xylitol) pH adjustment agents (NaOH or HCl).

CHARACTERIZATION TECHNIQUES OF NANOEMULSION:

- Nano-emulsions characteristics will depend on particle size, viscosity, density, phase inversion, turbidity, refractive index, skin permeation studies. Techniques used are:
- Thermal Conductivity Technique.
- Dynamic Light Scattering Spectrophotometer.
- Zeta Potential.
- Transmission Electron Microscopy (TEM).
- Drug Content.
- Viscosity Measurement.
- Phase Analysis Technique.

PREPARATION NANOEMULSION:

High-Energy (for laboratory and industrial preparation):

***For o/w and w/o emulsions*:**

***High-Pressure Homogenization*:**

In a high-pressure homogenizer, the dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion [30].

***Microfluidization*:**

Microfluidization is a mixing technique, which makes use of a device called a microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000 psi), and it forces the product through the interaction chamber, which consists of small channels called microchannels. The product flows through the microchannels onto an impingement area resulting in fine particles of the submicron size range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is inserted into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion. The premixed emulsion is circulated through the microfluidizer repeatedly until the required droplet size is achieved [31].

***Ultrasound emulsification*:**

In this method, a probe emits ultrasonic waves (20 kHz) to disintegrate the microemulsion by means of cavitation forces. By varying the ultrasonic energy input and time, the nanoemulsions with desired properties can be obtained. Undesirable for thermolabile drugs and macromolecules (Retinoids, proteins, enzymes, and nucleic acids).

Low-Energy (for lab preparation):

***Solvent diffusion 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 suitable means, such as vacuum evaporation.

***Phase Inversion*:**

In this method, fine dispersions are produced as the phase inversion occurs which is caused by varying the composition and keeping the temperature constant or vice versa.

Evaluation Parameters of Nanoemulsion System:

***Droplet size analysis*:**

Droplet size analysis of nanoemulsion was measured by a diffusion method utilizing the light-scattering particle size analyser (Nano ZS90, Malvern Pvt. Ltd. USA).

It is also measured by correlation spectroscopy which analyses the fluctuation in the scattering of light due to Brownian motion. Droplet size analysis of NE was also performed by Transmission electron microscopy (TEM) and Photon correlation spectroscopy (PCS) [32].

***Viscosity determination*:**
The Optimum viscosity is essential for a nanoemulsion system. The viscosity of nanoemulsion was measured by using Brookfield-type rotary viscometer at different shear rates at different temperatures [33].

***Drug content*:**
The drug content of the formulation was determined by using UV spectrophotometric and HPLC methods. In the case of UV, the 10 mg equivalent of drug-loaded nanoemulsion was dissolved in 100 ml of Solvent (A drug having optimum solubility of that solvent). From this stock solution, take 1 ml and dilute it in 10 ml of solvent (This solvent did not contain drug-loaded nanoemulsion). And Drug content was estimated at the reported Lambda max of that drug molecule [34].

pH:
The pH of the nanoemulsion System was measured by using a pH meter. (Systronic 362 µ pH system, India) [35].

Refractive index:
The refractive index of nanoemulsion was measured by Abbe's Refractometer. (Ningbo Biocotek Scientific Instrument, Ltd, Tokyo, China) [36].

Zeta Potential:
Zeta potential was measured by the charge on the surface of a droplet of Nanoemulsion. The formulation (0.1 ml) was diluted 100 times using double distilled water and analyzed using Zetasizer. (Nano ZS90, Malvern Pvt. Ltd. USA) [37].

Percentage transmittance:
The percentage transmittance of the optimized nanoemulsion formulations was determined spectrophotometrically using a UV spectrophotometer (Shimadzu 1700 and 2450, Japan) at the particular Lambda max of drug molecule [38].

Conductivity Test:
Conductivity analysis is a measure of how well a solution conducts electricity. Cleaning solutions are more conductive than water used for flushing the system, so conductivity measurement enables plants to monitor cleaning steps and final rinse to ensure completeness.

Dilution test:
Dilution of NE either with oil or water phase. The test is based on the dilution of the continuous phase of nanoemulsion without causing the problem of its stability. Thus, o/w NE is diluted with water, and w/o NE is diluted with oil [39].

Dye test:
The dye test measured the color uniformity of NE. in o/w NE water soluble dye was added to take up the color uniformity. If the NE is w/o type the dye being soluble in water, taken color only in the dispersed phase, and the emulsion was not uniformly colored. This can be revealed immediately by microscopic examination of the emulsion [40].

Polydispersity:
It indicates the uniformity of droplet size in nanoemulsion. The higher the value of polydispersity, the lower will be the uniformity of droplet size of nanoemulsion. It is measured by the Spectrophotometer.

Applications of Nanoemulsion:
- In cosmetics, Due to their lipophilic interior, nanoemulsions are more suitable for the transport of lipophilic compounds.
- High skin penetration due to small size.
- Antimicrobial Nanoemulsion.
- As a Non-toxic disinfectant cleaner.
- In cell culture technology.
- As a vehicle for Transdermal drug delivery.
- In cancer therapy and targeted drug delivery.
- As a mucosal vaccine, nasal route, Alzheimer's disease, migraine, depression,
- schizophrenia, Parkinson's diseases, meningitis.
- As a vehicle for an ocular delivery.
- Use of Nanoemulsions in Cosmetics.
- Improved oral delivery of poorly soluble drugs.
- Percutaneous Route.
- Pulmonary Delivery.

Commercial Nanoemulsions:
The nanoemulsions that are available in the market is given in Table 2.

CONCLUSION:
Nanoemulsions seem to be the most promising carriers for effective drug delivery. This review article investigates the potential herbs used to make nanoemulsion and to give the therapeutic effect to the patient, cost-effective, patient compliance, safe and effective. Nanoemulsions often have a higher loading capacity for lipophilic active ingredients than microemulsions, which can be an advantage in some applications.

The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase. Herbal medicine is the use of medicinal plants for illness prevention and treatment. It includes everything from traditional and popular remedies from all over the world to standardized and titrated herbal extracts.

Table 2. The commercial nanoemulsion (sub-micron emulsion) formulation.

Drug therapeutic	Brand name	Manufacturer	Indication
Propofol	Diprivan	Astra zeneca	Anesthetic
Dexamethasone	Limethason	Mitsubishi pharmaceutical Japan	Steroid
Palmitate alprostadil	Liple	Mitsubishi pharmaceutical Japan	Vasodilator platelet inhibitor
Flurbiprofen axetil	Ropion	Kaken pharmaceutical Japan	Nonsteroidal analgesic
Vitamins A, D, E, K	Vitalipid	Fresenius kabi Europe	Parental Nutrition

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