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A REVIEW–EVALUATION AND CHARACTERIZATION OF HERBAL NANOEMULSION

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ABSTRACT

The herbal medicines have been popularized throughout the globe since ancient time. Several plants based therapeutic moiety have been produced through new approaches. Many herbal bioactive have several health benefits but have limited therapeutic potential due to short biological half-life and moderate bioavailability profile. To improve such therapeutic issues nanocarriers were introduced such as phytosomes, ethosomes, transfersomes, herbal transdermal patches, nanoemulsion. They have the ability to maximize the efficacy of herbal bioactives by improving their solubility, absorption profile, lowering dose and side effects. Nanoemulsion is a mixing of oil, surfactant, co-surfactant and drug that can spontaneously form oil-in-water micro/nanoemulsion when mixed with water under continuous stirring. The solubility and bioavailability of nanoemulsion is achieved by its lipophilic nature and size reduction. The nanoemulsions can vehicle the herbal bioactive to the particular target site and offer sustained release of drug. The present review describes the importance of nanoemulsions for delivery of herbal drug.

KEYWORDS: Herbal, Nanoemulsion, Nanocarrier, bioavailability.

INTRODUCTION

In the past years, the use of herbal medicines has been increased due to their therapeutic effects and fewer side effects as compared to modern medicines. However, many herbal drugs and herbal extracts have low in-vivo activity due to their poor solubility, absorption and hence poor bioavailability, low stability or high metabolism.[1] Newer drug delivery systems showed good tools to formulate herbal drugs and to enhance their bioavailability. The novel formulations have amazing advantages over conventional formulations of herbal compounds and extracts, which increase of solubility, bioavailability, stability, improved of intracellular uptake, modification of pharmacokinetics and bio-distribution and sustained delivery possible. These methods not only apply to synthetic drug but also many isolated compound and herbal extract.[2&3] But the newly discovered phytopharmaceuticals have high molecular weight and classified into biopharmaceutical classification system IV, with poor water solubility and poor permeability characteristics. These limits to bioavailability of orally administered drugs.[4] Various techniques like Micronization, complexation, solid dispersion and permeation improver with surfactant have been used to overcome low solubility and intestinal permeation issues. Also use of novel drug delivery system like liposome, niosome, quantum dots, dendrimers, nanocapsule, phytosome, nanoparticles, suspension, nanoemulsion, etc are developed.[5] Nanoemulsions, also known as nanosize emulsions, ultrafine emulsions and miniemulsions, are submicron sized colloidal particulate systems considered as thermodynamically and kinetically stable isotropic dispersions of two immiscible liquids like water and oil, stabilized by an interfacial film consisting of a suitable surfactant and co-surfactant to form a single phase.

Three types of Nanoemulsions are mostly to be formed based on the composition:

1. Oil in water Nanoemulsions wherein oil droplets are dispersed in the continues aqueous phase
2. Water in oil Nanoemulsions wherein water droplets are dispersed in the external continuous oil phase
3. Bi-continuous Nanoemulsions wherein micro domains of oil and water are inter dispersed within the system.

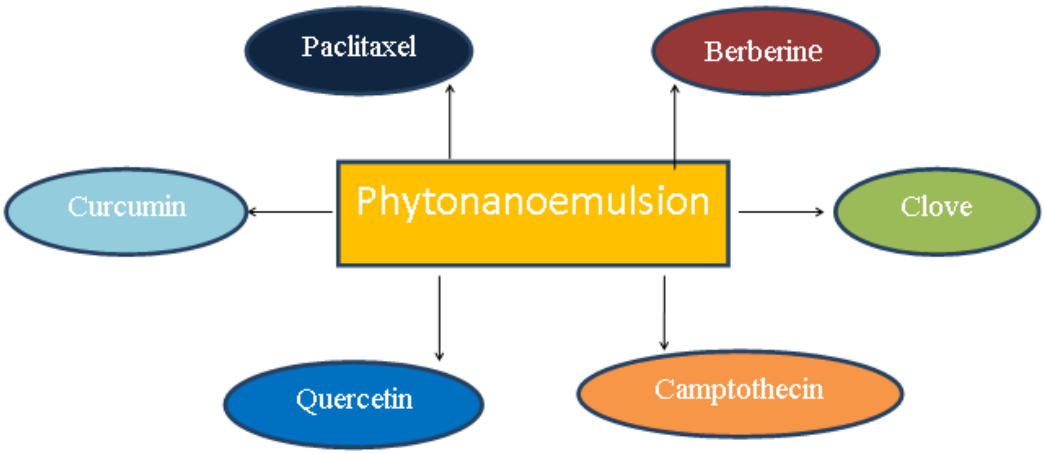

Figure 1: Graphical abstract.

All three types of Nanoemulsions is stabilized by an suitable combination of surfactants and/or co-surfactants[6] Due to high colloidal stability, smaller globule size and large surface area, nanoemulsions eliminate several problems like coalescence, sedimentation and flocculation that are associated with conventional emulsion formulation.[7&9] Global herbal medicine market is expected to reach more than USD 129 billion by 2023.[10]

Nanoemulsion possessing highest solubilizing capacity as compare to simple micellar solutions, leading to the incorporation of poor water-soluble phytopharmaceutical inside the lipophilic phase[11] Nanoemulsion used to avoid gastric degradation of herbal drug, maintain stability of natural product, facilitate sustained and targated drug delivery. The several phytoconstituents and herbal extract reported with nanoemulsion such as neem oil, eucalyptus oil, zedoary oil, curcumin, phaleria macrocarpa, citronella oil, capsicum oleoresin, berberine, triptolide, etc.[16] The interesting physicochemical belongings of nanoemulsion leads to use in different fields like medicine, agriculture, food, cosmetics, drug and diagnostics treatment.[12] Essential oils incorporated into nanoemulsion to improve transdermal permeation of drug across the skin. Chitosan is a natural polymer obtain from chitin, it is used asan encapsulating matrix because of its properties of biodegradable, renewable, nontoxic and aqueous soluble.[12&13] Nanoencapuslated ocimum sanctum with essential oil against aflatoxigenic fungi possesing novel mode of action as methyglyoxal inhibitor.[14] Herbal oil of petrodon emarginatuas microemulsion showed improved anti-inflammatory activity.[15]

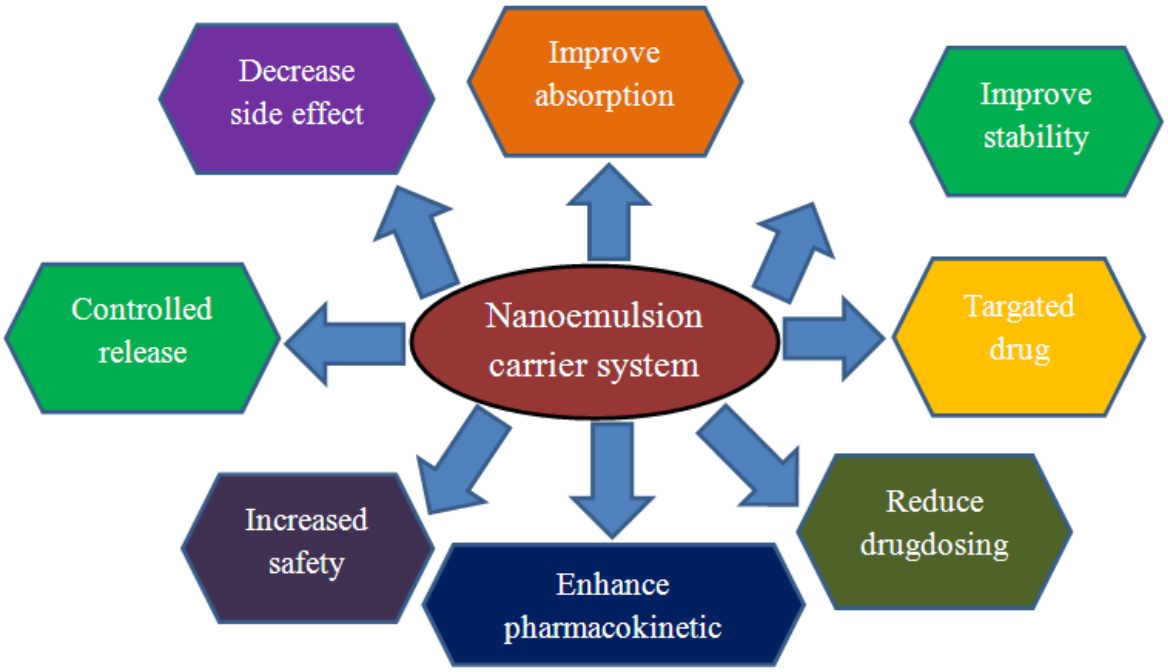

Figure 2: Different advantages of nanoemulsion.

Advantages Of Nanoemulsion

- Nanoemulsion is one of the best approaches to increase water solubility of the lipophilic drugs, which increases bioavailability of drug, also small droplet size increases surface area with improved transport property of herbal drug candidate.
- Nanoemulsions are also advantageously deliver peptides & proteins that metabolize by enzymatic hydrolysis.
- They reduce problem like creaming, flocculation, sedimentation, coalescence.
- It offers variety of formulation like transdermal patch, liquid, creams, gels, foams, sprays.
- Also use for veterinary therapeutic purposes.
- Increase the rate of absorption.

Applications Of Nanoemulsions

1. Nanoemulsions are used in intranasal drug delivery for the treatment of brain disorder such as alzheimer's disease, migraine, depression, schizophrenia, parkinson's diseases, meningitis, etc.
2. Nanoemulsions also applicable in transdermal drug delivery which increases absorption of drug across the skin, water-in-oil nanoemulsion formulations of caffeine have been developed for transdermal drug delivery.
3. Nanoemulsion is ideal vehicle for parenteral drug delivery, which dissolves large quantity of hydrophobic drug and protect drug from enzymatic degradation and hydrolysis.
4. Nanoemulsions serve as a tool for targeted & controlled drug delivery because of their small size they can easily tumor area and act as a vehicle for insoluble drug.
5. Nanoemulsions are promising carriers for DNA vaccines to the lung since they are able to transfect pulmonary epithelial cells without activating T- cell.
6. Use of nanoemulsion in cosmetic formulation.
7. Antimicrobial nanoemulsion.
8. Nanoemulsion for improving absorption and bioavailability of water insoluble drug.

Major Components Of Nanoemulsion

Oils: Selection of proper oil phase is very important as it determine the selection of other excipients of nanoemulsion usually in O/W type of nanoemulsion. Normally, the oil is selected which have maximal potential of drug solubilization. These aid to attain maximum drug entrapment in nanoemulsion. Constitution of natural oils and fats are mixtures of triglycerides. The selection of oil phase is commonly balance between ability to solubilize drug and ease of formulation of nanoemulsion of desired character. Thus,mixture of oil can cover both requirements. Modified vegetable oils, oils and fats such as palm oil, olive oil, corn oil, sesame oil, oleic acid, soybean oil, peanut oiland beeswax are also used as oil phase in nanoemulsion formulation.

Surfactants: The surfactant should favour emulsification of the oily phase and also possess good solubilizingproperty for the hydrophobic drug compounds. The selectivity of surfactant depends upon formulation development. Surfactants having HLB value <10 are hydrophobic (such as sorbitan monoesters) and form w/o nanoemulsion where as high HLB >10 surfactants such as polysorbate 80 are hydrophilic and form o/w nanoemulsion. In some cases mixture of hydrophobic and lipophilic surfactatntsare used to formulate nanoemulsion. Below critical micelle concentration of the surfactant increases solubility of drug. The surfactant used in nanoemulsion could be ionic or nonionic but ionic surfactant having toxic property so they are not preferly use in nanoemulsion formulation. Surfactant concentration plays important role in nanoemulsion, high concentration causes GI irritation. Sometimes it has showed that mean droplet size of globule increases with surfactant concentration.

Co-surfactant: Many times surfactant only unable to decrease the oil/water interfacial tension, in such cases fixed zero value of surface tension can be attaining by addition of co-surfactant. Co-surfactant penetrates the liquid rigid crystalline phase and increases liquidity of phase.Commonly low HLB value of cosurfactant is used mixed with high HLB value surfactant to adjust the final HLB of the system.Cosurfactants may not form micelle like surfactant. Hydrophilic cosurfactants preferably alcohols of intermediate chain length such as hexanol, pentanol andoctanol, which are known to reduce the oil/water interface and allow the spontaneous formation of nanoemulsion.

METHODS OF PREPARATION OF NANOEMULSION

Table 1: Different methods used in Nanoemulsion preparation.

Technique	Formulation	Finding	Reference no.
High Pressure Homogenization	Lipid nanoemulsion (Paclitaxel-baicalein)	Particle size 10-200nm enhance bioavailability	[3]
Spontaneous emulsification	Silybin nanoemulsion	Sustained release Particle size 21.20nm	[19]
Phase inversion temperature	Herbal nanoemulsion	Particle size 50nm	[26]
Sonication method	Quercetin loaded o/w nanoemulsion	Particle size 52nm	[18]
Self nanoemulsion	SNEDDS formulation of Persimmon leaf extract	Antioxidant activity	[27]
High-energy emulsification	β -carotene nanoemulsion	Influences the stability of Nanoemulsions	[4]

Nanoemulsions are prepared using various ingredients like surfactant those approved as safe by Food and Drug Administration for human internal use. Nanoemulsions having very fine globule size which can be achieved with help of high-pressure equipment. The most widely used methods for nanoemulsions are 'High-pressure homogenization' and 'Microfluidization' used in laboratory and industrial scale. Factors should consider while formulation nanoemulsion:

1) Surfactant must be selected precisely so that interfacial tension should controlled low at oil/water interface.
2) Amount of surfactant need to be sufficient to stabilize nano globules of emulsion.
3) The oil/interface should be fluid enough to promote nanoemulsion development.

1. **High Pressure Homogenization:** High-pressure homogenizer produces relatively very fine size emulsion. This device produces extremely small particle size up to 1nm by using high pressure and aids in nanoemulsion formulation. It forces the emulsion system through very small inlet at high-pressure (500 to 5000) resulting small size nanoemulsion. The two theories, turbulence and cavitation, describe the particle size in homogenization process. This method has special effectiveness, but have disadvantage of energy consumption and increase temperature during process.
2. **Ultrasonication:** It is one of the first applications of ultrasound to prepare emulsion patent has been filed for this techniquefifty years ago. Cavitation is the major mechanism in which build up and breakdown of vapour cavities in contentious liquid takes place. The oil phase is mixed with contentious phase in the form of globule with the help of acoustic field. Commercially this technique is not available to nanoemulsion production.
3. **Microfluidization:** It is a mixing method consist a device called microfluidizer. This device attached with high-pressure positive displacement pump, which passes the system in interaction chamber, which made up of small channel called microchannel. The system moves through the microchannels on to an impingement area producing very small fine particle of submicron range. The coarse emulsion passes through interaction chamber until desired size is achieved.
4. **Spontaneous Emulsification:** Spontaneous emulsification has been achieved by pouring, into aqueous phase, a solution comprising a little oil in water miscible dissolved and without surfactant. The organic phase is needed to be injected in the aqueous phase with constant stirring resulted in o/w emulsion. The water miscible solvent is removed by evaporation. This is alternative method to ultrasonication and high-pressure homogenization.
5. **Phase Inversion Technique:** Nanoemulsion preparation using these technique does not require any special force of application, it just prepared by phase transition with the help of altering temperature and changing components and keeping all other parameter constant of the system.
6. **Hydrogel Method:** It is same as solvent evaporation method. The only difference is drug solvent is miscible with drug antisolvent. High shear pressure reduces the chances of crystal growth and Oswald ripening.

Characterization Of Nanoemulsion

1. **Nanoemulsion Droplet Size Analysis:** Measurement of droplet size is important physicochemical properties of nanoemulsion and its measurement carried out by using diffusion method using a light scattering particle size analyzer Coulter LS-230analyzer Coulter LS-230. It determines the particle size distribution using the diffusion of laser light by particles. Polarization intensity differential scattering (PIDS) is the construction consists of an light source and polarizing filters, a PIDS sample cell and an additional photodiodedetectors. It is used to determine the globule size distribution, like 0.5 ml nanoemulsion was introduced in the measure compartment (125 ml of water).

2. **Polydispersity index:**The particle size and polydispersity index are measure by using photon correlation spectroscopy (PCS) employing Malvern Zetasizer which determine the difference in light scattering because of Brownian motion of particles with time.PCS work on the basis of principal that small particle travel with higher velocity as compared large particle. The PDI range between 0 to 1, where zero stands for monodisperse system and one for a polydisperse particle dispersion. The particle size and PDI measurements are carried out at 25 degree celsiususing a He-Ne laser.
3. **pH:** The apparent pH of the formulation is measured by pH meter.
4. **Transmission Electron Microscopy:** The morphological study of nanoemulsions is carried out by using transmission electron microscopy and scanning electron microscopy, an incident beamreveals the particle size characteristics of nanoemulsion droplets. Observations was performed as, a drop of the nanoemulsion was deposited directly on the holey film grid and observed after drying.
5. **Drug Content:** Drug content was determined by reverse phase HPLC method using C18 column.
6. **Zeta Potential:** Zeta potential is a method helps to determine surface charge properties and further stability study of nanoemulsion. The equipment, which is used to determine the surface charge, is known as Zeta PALS. The determination was done with diluted nanoemulsion and its values were measure from the electrophoresis mobility of the oil droplets. The desirable value of zeta potential should be of ±20mv.
7. **Percentage Transmittance:** Percentage transmission determination of nanoemulsion was carried out by using UV-VIS spectroscopy. If transmittance of a nanoemulsion is found to be greater than 99%, then it is considered as transparent in nature.
8. **Dynamic Light Scattering Spectrophotometer:** Dynamic light scattering spectroscopy determination carried out at 90°with the help of neon laser of wavelength 632nm. The particle size and particle size distribution are measured by dynamic light scattering spectrophotometer.
9. **Dye Solubilization:** A water-soluble dye is dissolved in the aqueous phase of the w/o globule but is dispersible in the o/w globule. An oil soluble dye is dissolved in the oil phase of the o/w globule but is dispersible in the w/o globule.
10. **Dilution Test:** O/Wnanoemulsions are dilute with water and in other hand w/o are not and undergo phase inversion into o/w nanoemulsion.
11. **Conductance Measurement:** The O/W nanoemulsion are highly conducting because they have external aqueous phase whereas W/O nanoemulsions are not conducting as they havewater in internal phase. Electrical conductivity measurements are important for determining the type of the continuous phase and for detect phase inversion phenomenon.
12. **Fluorescence test:** Use to detect the emulsion type if a W/O nanoemulsion is exposed to a fluorescence light under a microscope, the whole field will fluoresce and if it is O/W the fluorescence will be in spots.
13. **In Vitro Skin Permeation Studies:** Franz diffusion cell is used to study the drug release pattern of herbal nanoemulsion formulation in the case of topical application. The extent of skin penetration depends on the release component of and visualization done with the help of confocal scanning laser microscopy. In vitro drug release carried out by distributing the drug in donor compartment of Franze diffusion cell consist of membrane barrier and determine the loaded drug observed in receptor compartment, commonly contents phosphate buffer with continuous stirring. The drug dispersion of receptor donor wasreplaced by equivalent quantity of the medium at particular time interval. The sample withdraw from receptor donor is filtered by 0.22-50µm filter and drug analysis is done by HPLC and UV-Vis spectroscopy.

CONCLUSION

This review is focused on advantages ofnanoemulsion as drug delivery vehicle for herbal drug candidate. Nanoemulsions showscountless advantages for the delivery of drugs, herbal extract, bioactive compound, diagnostic agents and increase solubility, enhance bioavailability of natural origin drug.Nanoemulsions have skin penetration properties and less irritancy so act as good carrier for topical drug delivery. Nowadays nanoemulsion receives great importance of targeted drug delivery in various anticancer drug therapies. Also, serve carrier for water insoluble drug candidate. Because of their submicron size, they can easily targettumor. It is suggested that future work can be done for clinical understanding of targeted delivery vehicles.

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