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A Comprehensive Review on: Herbal Nanoemulsion Formulation, Characterization and It's Application



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ABSTRACT

In the present review work, we discuss the role of herbal nanoemulsion to produce the therapeutic effect to treat different types of diseases condition from milder to severe. Herbal drugs have fewer side effects or no side effects and it having the ability to treat various types of disease condition that's why in the future we plan to formulate herbal drug extract into nanoemulsion. The development of pharmaceutical drugs, nutraceuticals, food items, and cosmetic formulations is very interesting in nanoemulsion formulation. Because nanoemulsion has an advantage over different formulations so nanoemulsion techniques commonly employs for drug delivery systems for the administration of medication. Nanoemulsion is a formulation having a particle size ranging from 50 -1000nm. This system offers extended release of herbal drugs and also improve the therapeutic effect of poorly aqueous soluble herbal drug. The present review highlights the development of nanoemulsion for plant active constituents as well as their preparation method, components, their evaluation and it's herbal application. In the present review work we discuss various methods mainly used to formulate the herbal nanoemulsion.

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INTRODUCTION

In current trends interest has been directed toward lipid base formulation to increase the permeability and bioavailability of drugs by using novel drug delivery systems like nanoemulsion plays an important role in delivering the herbal formulation at the target organ. Amongst all other techniques nanoemulsion shows better development in drug delivery of herbal ingredients. The nanoemulsion is said to be a thermodynamically stable, isotropically transparent dispersion of two immiscible liquids such as oil and water surfactant stabilizer. The oil in water and water in oil emulsion with droplet size 50 to 1000nm. The alternative names of emulsion, mini emulsion, sub-micron emulsion, and ultrafine emulsion. Nanoemulsions were prepared by both the high energy emulsification method and the low energy emulsification method. High energy method mainly denoted high shear mixing, high-pressure ultrasonication, while low energy emulsification mainly used to physicochemical properties of the system which produce nanoemulsion. The oil, surfactant, and co-surfactant are mainly non-toxic, non-irritant, and mainly suitable for consumption by human so to increase the therapeutic effect of the herbal drugs as formulated into herbal nanoemulsion to reach the site of action.^[1-3]

Table no .1.Component's mainly used to formulate herbal Nanoemulsion^[4]

| Sr.No. | Component | Example | Role |
|--------|---------------|---|--|
| 1 | Oil | Palm oil , olive oil,sesame oil , hydrogenated soyabean oil , peanut oil | Solubilizing potential. |
| 2 | Surfactant | Polysorbate20, polysorbate80, polyoxy60, castor oil,PEG300,caprylic glyceride | Minimizes the interfacial tension of oil and water, acts as the emulsifier in the formulation. |
| 3 | Co-surfactant | Ethanol, glycerin PEG300 , PEG400,polyene glycol | Lower the interfacial tension. |
| 4 | Co-solvent | Glycerol, polyethylene glycol, ethanol, propylene glycol | To dissolve a large amounts of water-soluble surfactant and active constituents. |

Available methods for preparation of herbal nanoemulsion

1. Production of Phyto-Nanoemulsion

Herbal oils prepared using a new and effective extraction methods, were used to develop emulsion based for simulations. Oil in water nanoemulsions (F1 and F 2) were produced with different percentages of an oil phase and aqueous phase. Nanoemulsions containing *Calendula* infused black seed oil as the dispersed phase and distilled water as the continuous phase was prepared using emulsifying agents including Lecithin and Tween80 dissolved in the oil phase and aqueous phase respectively. F1 formulation contains 20wt.% *Calendula* infused Black seed oil (with 3.0wt.% Lecithin) and 80wt.% aqueous phase (with 3.0wt.% Tween) besides F2 formulation contains 40wt.% *Calendula* infused Black seed oil (with 3.0wt.% Lecithin) and 60wt.% aqueous (with 3.0wt.% Tween80). Both formulations were homogenized using an ultrasonic processor (Vibra cell, VCX500, Sonics & Material, Inc., Newtown, USA) for 10min with an amplitude of 40%. To prevent any thermal damage, all formulations were produced in an ice bath during the Ultrasonication process. The obtained Phyto- Nanoemulsion was kept at +4°C in dark for further bioactivity investigation.^[5]

2. Preparation of Vegetable oil based nanoemulsion containing curcuminoids

Nanoemulsion and curcuminoids loaded nanoemulsion were prepared by the formation of microemulsion at its phase inversion temperature method followed by immediate cooling to room temperature. Briefly, nanoemulsions were prepared by simple mixing of all components at ambient temperature and gently heating to 90 °C on a hot plate magnetic stirrer with continuous stirring followed by cooling down to 60°C. To perform the inversion process, 3 temperature cycles (90-60-90-60-90°C) were applied. During the third cycle, when the temperature decreased to 75° C where the system appeared translucent with blue glints, the system was rapidly cooled by dilution with twice the amount of cold water. Afterward, a continuous magnetic stirring was applied to the emulsion for 5min.^[6]

3. Preparation of Baicalin nanoemulsions

The nanoemulsion formulation composed of soy-lecithin, tween-80, PEG400, IPM, and water (1:2:1.5:3.75:8.25w/w) was selected and developed into baicalin-loaded nanoemulsions. Baicalin was first dissolved in PEG400 and mixed with soy-lecithin, tween-80, IPM after which the required amount of water was added and the solution stirred to obtain clear and transparent liquid i.e. baicalin – loaded nanoemulsion (BAN-1). The resulting nanoemulsion

was filled with nitrogen gas and tightly sealed and stored at room temperature. In addition, Baicalin was dissolved in the final nanoemulsion formulations to obtain baicalin-loaded nanoemulsion(BAN-2).^[7]

4. Preparation of nanoemulsion containing the *Rapanea ferruginea* soft extract

A nanoemulsion was developed from a pseudo ternary phase diagram using PEG-40 hydrogenated castor oil and sorbitan oleate as surfactant and isopropyl myristate as oil. The oil phase, containing 0.13% *R.ferruginez* dissolved in propylene glycol (2%), isopropyl myristate(20.0%),PHCO + sorbitan oleate (7.2:1.5) (13.3%), and preservative 0.75% was heated to 80° C. The aqueous phase(65.95%water,80° C) dropped while stirring at 600rpm and 80° C. After 5 min the heating was stopped and the formulation was stirred for 3 min. After cooling Sepigel (0.85%) was added and the nanoemulsion was placed in an aluminum-coated tube.^[8]

Types of Nanoemulsion

1. Oil in water nanoemulsion
2. Water in oil nanoemulsion
3. Bi-continuous nanoemulsion^[9]



Methods For Preparation of Nanoemulsion^[10]

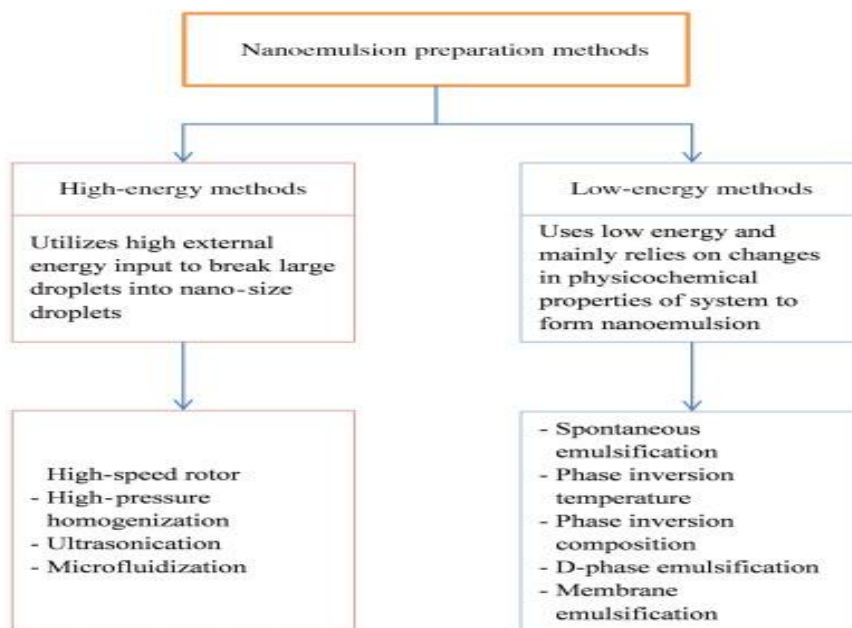


Figure no .1. Methods For Preparation of Nanoemulsion

A.High energy method

High mechanical energy is an important source to create powerful disruptive forces that convert large droplets into Nano-size droplets and which result in the preparation of highly dynamic nanoemulsions. This type of disruptive force can be produced by using Ultrasonication, microfluidizer and high-pressure homogenizers. This is a conventional mechanical method because nanoemulsion prepared using ultrasound requires less amount of surfactant and it is cost-effective technique. ^[11-15]

High-pressure homogenization

This is the most commonly used method for the development of nanoemulsion. In this method very small-sized droplet (up to 1 μ m) nanoemulsion can be produced using intensely disruptive forces developed by high-pressure homogenizer. This method is unsuitable for the production of creamy or highly viscous nanoemulsion having nanoparticle diameter less than 200nm. A system has a sufficient amount of surfactant which results in the development of nanoemulsion having particle size of about 50-350nm.

Micro-fluidization

Wider and small particle size nanoemulsion produced through micro-fluidization technique as compared to homogenization method. Also, at very low concentrations of surfactant microfluidizer produce stable nanoemulsions. Microfluidizers are costlier than other equipment and not suitable for large-scale manufacturing.

Ultrasonication

In this emulsification process, ultrasound waves develop cavitation forces which result in the conversion of macroemulsion into nanoemulsion. This emulsification process involved two types of mechanism.

1. Interfacial waves developed by acoustic field and this wave is unstable resulting in the oil phase exploding in the aqueous phase as a droplet.
2. Acoustic cavitation develops by low-frequency ultrasound. Disruption of a primary droplet of dispersed oil into less than micron size droplet by turbulent micro-implosions.

B.Low energy methods

Nanoemulsion preparation can be done using the low energy emulsification method. For the production of Nano-sized droplets using low energy method mostly depends on the modification of interfacial phase transition phenomena and the physicochemical properties of surfactant, co-surfactant, and oil. This method has the advantages to develop very small size particles than high energy methods and has disadvantages to the use of oil, emulsifiers Ex-proteins, and Polysaccharides this problem solve using a synthetic surfactants.

Phase inversion temperature (PIT)

PIT this method involves altering the HLB of nonionic surfactant with temperature or altering surfactant curvature due to temperature. According to temperature-dependent solubility, this method can change the affinity of non-ionic surfactants towards oil and water depending on their temperature ex- Polyethoxylate surfactant. The most important advantage of phase inversion temperature over the phase inversion composition method is having high emulsification efficiency and low polydispersity index.

Phase inversion composition (PIC)

Phase inversion composition this method involved the preparation of a Nano-sized emulsion without the use of any organic solvent & heat at room temperature. During this process of emulsification, the continuous phase component is slowly added to the dispersed phase components. PIC method Nano-sized emulsion droplets with the incorporation of solvent or energy-intensive method like High energy approach at room temperature.

Spontaneous emulsification

Also, another technique for the production of Nano-sized droplets is spontaneous emulsification. For the creation of nanoemulsion-through the spontaneous emulsification method which uses chemical energy that produces in the dilution process and without any phase transitions inside the system maintaining the continuous phase and constant temperature.

Solvent displacement method

In this method for spontaneously producing nanoemulsion which has been affected by Nano-precipitation process to produce polymeric nanoparticles. For a generation of monodisperse

small-sized polymeric nanoparticle solvent displacement method has advantages like reproducible, inexpensive, one-step manufacturing processes and appropriate.^[15-19]

Advantages of Nanoemulsion

1. Decrease the absorption variability.
2. It increases the solubility of the drug.
3. It masks the unpleasant taste.
4. Drug delivery through various routes possible like oral and topical.
5. It provides rapid penetration through the skin.^[20]

Disadvantages of Nanoemulsion

1. Large amount of surfactant and co-surfactant require to stabilize the emulsion.
2. Environmental factors affect the stability of formulation and also change in pH.
3. It must be non-toxic.^[21]

After the preparation of the nanoemulsion it is necessary to evaluate the herbal nanoemulsion to meet all specifications of the prepared nanoemulsion by using different parameters following are the important parameter for the evaluation of herbal nanoemulsion. These all parameter gives the idea about prepared nanoemulsion meets or does not meet the required parameter for further development of nanoemulsion.

Table.no 2. Evaluation parameter for Nanoemulsion

| | | | |
|------------------------|------------------|------------------------|---------------------------------|
| Particle size analysis | Zeta potential | Rheological properties | Drug content |
| pH | Refractive index | Phase behavior study | Thermodynamic Stability Studies |

The role of Nanoemulsion in the delivery of herbal medicines

For oral administration of herbal medicament which is low bioavailable, its bioavailability and permeability increased by using a nanoemulsion system. Nanoemulsion is harmless for humans due to that oils, and lipids are easily absorbed and are nontoxic, and safe for the human body. Nanoemulsion can also increase the stability of the formulation. Nanoemulsion

is an important method for the accurately delivery of herbal medicament via the skin for ex-Catechin, epicatechin, gallate, ferulic caffeine, acid, and Curcumin. Nanoemulsion is a most important technique because it can interact with the fluidic and emulsifier nature of skin cells at the interface. For delivery of volatile, irritant, and high molecular weight medicament the nanoemulsion is the greatest technique to deliver those medicaments. For targeting and accurate delivery of herbal phytoconstituent a different route of administration a nanoemulsion technique is most effective. Due to high surface changes in nanoemulsion, it improves efficacy and interaction. Lowering the dose of medicament, solving drug toxicity issues and increasing the therapeutic effect of the herbal drugs can be achieved by using nanoemulsion. For delivery of a medicament, essential oil used as an antibacterial, repellent, and nucleic acid nanoemulsion is the most suitable method.^[22-23]

Table. No 3. Some example of herbal nanoemulsion formulation.^[24-31]

| Sr. No. | Herbal extract | Method of preparation | Therapeutic activity | Application of nanoemulsion |
|---------|---|--|--|---|
| 1 | Curcumin extract nanoemulgel | Low energy emulsification method | Long term management of psoriasis | Improve solubility & skin penetration after the topical administration |
| 2 | Linseed oil nanoemulsion | Ultrasonic emulsification method | Atopic dermatitis disease | Highest stability |
| 3 | Quercetin nanoemulsion | Ultrasonication method | STZ-induced diabetes (antidiabetic activity) | Good stability, oral bioavailability |
| 4 | Boswellic acid nanoemulsion based hydrogel | Homogenization | Anti-inflammatory effect on rats using carrageenan induced rat paw edema model | Improve skin permeation ability, increasing bioavailability |
| 5 | O/W nanoemulsion of mint essential oil and parsley aqueous extraction | Homogenization | Antibacterial activity | Prevent particle growth with the low cytotoxicity suitable stability |
| 6 | Vitamin E loaded naringenin nanoemulsion | Aqueous titration method | Parkinson's disease, antioxidant activity | Nanoemulsion enhance deliver to the brain via intranasal route avoiding first pass metabolism |
| 7 | Silumarin nanoemulsion | High pressure homogenization technique | Hepatic disorder | Improving oral bioavailability |
| 8 | Thymus vulgaris essential oil nanoemulsion | High-pressure homogenization | Antimicrobial activity | Increasing solubility of oil |

CONCLUSION

The present review concludes that nanoemulsion is a most important technique which makes the herbal drug more bioavailable and produces potent therapeutic effect to treat several disease conditions. Mainly two methods used to formulate the herbal nanoemulsion like High and low energy methods is incorporated for the creation of nanoemulsion and both methods can produce stable nanoemulsion. Now day's nanoemulsion is produced for delivering a drug through a different routes of administration. Nanoemulsion can deliver and produce the formulation as an efficient, safe, and patient-compliance formulation and it improves the stability of the formulation. Herbal drugs show less or no toxic effect on the human body that's why it is helpful to formulate herbal drugs into nanoemulsion. By regulating the concentration of surfactant, and co-surfactant, and types of oils phase nanoemulsion method involved variation in the process. From this, we conclude that in the future we formulate some herbal drugs into nanoemulsions to explore it for their better therapeutic activities.

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