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A REVIEW ON PREPARATION AND EVALUATION OF NANOEMULSION

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ABSTRACT

Nanoemulsion Considers a novel drug delivery System that permits Controlled or sustained drug release. It is a dispersion consisting of a Surfactant, oil, and clear aqueous phase. Kinetically, or thermodynamically stable, droplet diameter 10-100mm. Nanoemulsion applied to increase the Solubility and bioavailability of Lipophilic drug. This review provides brief information about method of preparation and evaluation of nanoemulsion as drug Carriers for improving the delivery of therapeutic agents. Several techniques are to be used for preparation of Nanoemulsions Like High pressure homogenization, microfluidization, ultrasonication, Solvent evaporation Method, and parameters that are to be used for its. Characterization like Dry Solubilization, Polydispersity, Phase analysis, Interfacial tension, Viscosity, P^H, Refractive Index, TEM, In- Vitro Skin Permeation Study.

KEYWORDS: Nanoemulsion, microfluidization, ultrasonication, Dry Solubilization, Polydispersity.

INTRODUCTION

Nanotechnology it is the preparation of the nanosized structures containing the drugs. The definition of nanotechnology it is study and structures in the size range of 1-100nm. In the nanotechnology other important drug delivery system it will be developed that is Nanoparticles, SLNs, Nanosuspension, NLCs, Nanoemulsion, Nanocrystals, LDCs etc. This review focused on the Nanoemulsion for drug delivery and targeting application. NEs are a group of dispersed particles used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. NEs can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm. The particles can exist as water-in-oil and oil in water forms, where the core of the particle is either water or oil, respectively. The NEs

are also referred as Miniemulsions, ultrafine emulsions and submicron emulsions. Phase behavior studies have shown that the size of the droplets is governed by the surfactant phase structure at the inversion point induced by either temperature or composition. Studies on NE formation by the phase inversion temperature method have shown a relationship between minimum droplet size and complete solubilization of the oil in a microemulsion bicontinuous phase independently of whether the initial phase equilibrium is single or multiphase, Nanoemulsions are part colloidal dispersions of two immiscible liquids. Nanoemulsion possesses stability of outstanding application like it waiver the destabilization process of emulsion i.e., creaming. flocculation, coalescence and sedimentation, 10 Mainly GRAS (Generally regarded as safe) Nanoemulsion, formulated with oil, surfactant and co-surfactant are nontoxic, nonirritant and approved for human consumption that are "generally recognized as safe" by the FDA.

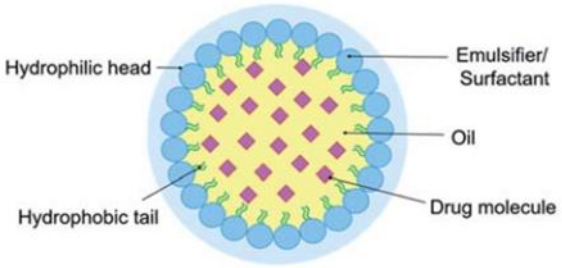

Fig No 1: Nanoemulsion.

ADVANTAGES

i. It aids in the solubilization of lipophilic drugs
ii. Useful for flavor masking
iii. There is less energy required
iv. It has increased physical stability
v. It is available in a range of formulations includes foams, creams, liquid and sprays
vi. It improves the absorption of oil-soluble nutrients in cell culture technology.

DISADVANTAGES

i. It required the use of surfactant and co-surfactant in large concentration. That Are essential for stability.
ii. Low solubility capacity for high melting materials.
iii. Surfactant and co-surfactant used should be nontoxic

COMPONENTS OF NANOEMULSION

Main Three Components of NEs are as Follows:

1. Oil
2. Surfactant / Cosurfactant
3. Aqueous Phase

Oil

The oil selection used in Nanoemulsion formulation considers as an important factor since the drug will be incorporated as a droplet in the oily phase that dispersed in the aqueous phase. So, the oil which is selected should able

to dissolve the substances used in dosage form to get a higher % of drug-loaded, also oil selected must be compatible with other Nanoemulsion component. The oil used in Nanoemulsion either natural, synthetic, or semi-synthetic.

Surfactant: (surface-active agent)

Surfactants are substances that decrease interfacial tension or surface tension occurring between a solid and a liquid. Surfactant act either as an emulsifier, wetting agent, foaming agent, detergents, and dispersants, which depending on hydrophilic-lipophilic balance (HLB) value. The use of surfactant in preparation of Nanoemulsion to stabilize the system and chooses it to depend on Nanoemulsion type to be prepared Hydrophilic Surfactant with HLB value more than 10 used for o/w nanoemulsion, while hydrophobic Surfactant with HLB value less than 10 used for w/o Nanoemulsion. The use of Surfactant combinations with low and high HLB value leading to the formation of good stability Nanoemulsion upon water dilution.

Co - Surfactant

These materials added to Nanoemulsion formulation to decrease the interfacial tension that occurs between oil and water when the surfactant failed to decrease it. In addition, it provided some fluidity to the interfacial tension of Surfactant when it has high rigidity, through penetrating into a monolayer of surfactant and disrupting its crystalline liquid phase, an example of Co-Surfactant propylene glycol, poly glyceryl oleate, PEG400.

Aqueous phase

Deionized water used in Nanoemulsion formulation as an aqueous phase since its pH 7 and has no electrolytes. The stability of Nanoemulsion and its droplet size influenced by the nature of aqueous phases like ionic content, electrolytes, and pH. The electrolyte decreases the repulsion force between droplet due to zeta potential reduction and pH changing of formulation leading droplet flocculation in the formulation.

Different techniques for preparation of nanoemulsion

1. High -pressure homogenization
2. Low -pressure homogenizer
3. Microfluidization
4. Ultrasonication
5. Spontaneous emulsification
6. Phase inversion method
7. Method Hydrogel
8. Phase inversion temperature

1. High -pressure homogenization: The popular method for production nanoemulsion involves using a high-pressure homogenizer to produce nanoemulsion with particle sizes upto 1nm. The process involves forcing the macroemulsion through a small orifice at a 2 pressure between 500 to 5000 psi, resulting in extremely small droplet sized nanoemulsions. This process can be repeated until the final product reaches the desired droplet size and polydispersity index [PDI], which specified the uniformity of droplet size in nanoemulsions.

High-pressure homogenizer are commonly used to prepare nanoemulsions, generating nanoemulsions of extremely low particles size upto 1 nm. These nanoemulsions are formed through intense forces, such as turbulence hydraulic shear,

and cauiration and their particle size depend on sample composition, homogenizers,microfuidizers, and ultrasonication to produce micro droplets.These method require sophistication equipment and energy consumption, but offer large component selection and control. However, they are expensive and not suitable for thermos -labile active ingredients or macromolecules.

2. **Low -pressure homogenizer:** Low-how-energy emulsification methods are energy efficient and involve phojeinvesion emulsification and Self emulsification. These methods are not suitable good for food grade nanoemulsions due to high Surfactant concentration which can affect taste and safety. Phase Inversion emulsification Involves Spontaneous curvature of surfactant, with two types: TPI (PIT and PIC) + CPI (EIP). Transitional phase inversion occurs due to changes in Surfactant affinity, while Catatrophic phase inversion occurs when the Surfactant is primarily present in the dispersed phase, leading to rapid phase inversion. Nanoemulsion can be acheived using low energy methods, resulting in smaller, more uniform droplets. However these methods have limitations due to the use of certain oils and Emulsifier like proteins and polysaccharides. To overcome this high synthetic surfactants Concentrations are used in low-energy techniques, limiting their applications food processes".

3. Microfluidization: Microfluidic methods enable controlled formation of liquid droplets and gas bubbles microchannels, allowed for the creation of lab-on-a chip devices. By transferring microquantities of liquid in droplets and bubbles through microchannels to precise places these devices miniaturice chemical and biological processes. Protein isolation, DNA analysis, enzymeencapsulation, and biosensor development are all being investigated. Emulsification happens in minoFtuidizers due to collision of two immiscible fluid flow stream travelling in microchannels under high pressure Ythe wetting of channel walls by emulsions components determines the stability of emulsification icons regime. microfluidizer have three fundamental flow stream configurations:

1. Co-directional
2. Opposite directional
3. T-Shaped interaction.

These combinations result in single drops of varied diameter. High pressure propels in the interaction chamber, producing nanoemulsions with submicro particles sizes. By repeating the process and modifying the operation pressure, uniform nanoemulsion production can be accomplished. A pneumatically powered pump allows crude emulsions to move, resulting in strong shearing Force and the formation of fine emulsion.

4. Ultrasonication: In this technique premixed emulsion is exposed to agitation at ultrasonic frequency of 20 kHz reducing the droplets to nanodroplets size. The resultant emulsion is then passed through high shear region to form droplets with uniform size distribution. Water jacket is employed in this technique to regulate the temperature. Sonotrodes also known as sonicator probe consisted of piezoelectric quartz crystals as the energy providers during ultrasonic emulsification. On application of alternating electric voltage, these sonotrodes contract and expand. Mechanical vibrations are produced when the sonicator tip contacted the liquid resulting in cavitation, which leads to collapse of vapour cavities formed within the liquid. This technique is mainly adopted when droplet size less than 0.2 μ is required. Shiet al. formulated emodin-loaded nanoemulsion by using ultrasonic emulsification method at a frequency of 25 kHz and achieved mean diameter of emodinloaded nanoemulsion was found to be in the range of 10-30 nm.

5. Spontaneous emulsification: This technique involved preparation of nanoemulsion in 3 stages. The first stage included formation of an organic solution, comprising of oil and lipophilic surfactant in water miscible solvent and hydrophilic surfactant and then the O/W emulsion is formed by injecting this organic phase into the aqueous phase under magnetic stirring. The organic solvent was then removed in the third stage by evaporation. Sugumar et al. formulated stable eucalyptus oil nanoemulsion by adopting spontaneous emulsification and the mean droplet size was found to be in the range of 50-100 nm.

6. Phase inversion method: In this method, fine dispersion is obtained by chemical energy resulting of phase transitions produced by emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping temperature constant or vice versa. The phase inversion temperature was first done by Shinoda et al. it was concluded that increase in temperature results in the chemical changes of polyoxyethelene surfactants by degradation of the polymer chain with the temperature.

7. Method Hydrogel: It is similar to solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevent crystal growth and Ostwald ripening.

8. Phase inversion temperature: The Temperature of phase Inversion [PIT] approach modulates temperature while retaining composition, which is particularly useful for non-ionic surfactants such as polyethoxylated surfactants. Emulsification happens when the affinities of surfactants for water and oil change with temperature. Polyoxyethylene groups become lipophilic as they dehydrate during heating. The PIT method is used to make nanoemulsions by heating the sample to the PIT or hydrophile-lipophilebalance (HLB) level. Oil-in-water (O/W) emulsions are created by combining oil, water, and nonionic surfactants. Surfactant POE groups dehydrate as the temperature rises, generating phaseinversion and the formation of water-in-oil (W/O) nanoemulsions. For efficient phase inversion, rapid cooling or heating is essential.

CHARACTERIZATION OF NANOEMULSION

Characterization of Nanoemulsion

The droplet size, viscosity, density, turbidity, refractive index,phase separation and pH measurements shall be performed to characterize the Nanoemulsion. The droplet size distribution of Nanoemulsion vesicle can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting Nanoemulsion stability.

Dye Solubilization

A water soluble dye is solubilized within the aqueous phase of the W/O globule but is dispersible in the O/W globule. An oil soluble dye is solubilized within the oil phase of the O/W globule but is dispersible in the W/O globule.

Dilutability Test

O/W Nanoemulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W Nanoemulsion.

Polydispersity

The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements were performed at 250C using a He-Ne laser.

Interfacial Tension

The formation and the properties of Nanoemulsion can be studied by measuring the interfacial tension. Ultra-low values of interfacial tension are correlated with phase behaviour, particularly the existence of surfactant phase or middle-phase Nanoemulsions in equilibrium with aqueous and oil phases. Spinning-drop apparatus can be used to measure the ultra-low interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.

Viscosity measurements

The viscosity of Nanoemulsions of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37±0.2°C by a thermobath, and the samples for the measurement are to be immersed in it before testing.

pH

The apparent pH of the formulation was measured by pH meter.

Refractive Index

The refractive index, n, of a medium is defined as the ration f the speed, c, of a wave such as light or sound in a reference medium to the phase speed, vp, of the wave in the medium. n=c/vp; It was determined using an Abbes type refractrometer (Nirmal International) at 25+0.5°C.

Transmission Electron Microscopy [TEM]

Morphology and structure of the nanoemulsion were studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of nanoemulsion droplets. Observations was performed as, a drop of the nanoemulsion was directly deposited on the holey film grid and observed after drying.

In Vitro Permeation Studies

In vitro skin permeation studies were performed by using Keshary Chien-diffusion cell. It was performed on abdominal skins and was obtained from male rats weighing 250±10 gm with a recirculating water bath and 12 diffusion cells. The skins were placed between the donor and the receiver chambers of vertical diffusion cells. The receiver chambers were filled with freshly water containing 20% ethanol. The receiver chambers were set at 37oC and the solution in the receiver chambers was stirred continuously at 300 rpm. The formulations were placed in the donor chamber. At 2, 4, 6, 8 h, 0.5 ml of the solution in the receiver chamber was removed for GC analysis and replaced immediately with an equal volume of fresh solution. Each sample was performed three times 7. The cumulative corrections were made to obtain the total amounts of drugs permeated at each time interval. The cumulative amounts of drug permeated through rat skins were plotted as a function of time. The permeation rates of drug at a steady-state through rat skins were calculated from the slope of linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot.

Thermodynamic Stability Studies

During the thermodynamic stability of drug loaded Nano-emulsions following stress tests as reported:

a. **Heating Cooling Cycle:** Nanoemulsion formulations were subjected to six cycles between refrigerator temperature (4°C) and 45°C. Stable formulations were then subjected to centrifugation test.
b. **Centrifugation:** Nanoemulsion formulations were centrifuged at 3500 rpm and those that did not show any phase separation were taken for the freeze the stress test.
c. **Freeze Thaw Cycle:** In this the formulation were subjected to three freeze thaw cycles between 21°C and +25°C kept under standard laboratory conditions. These studies were performed for the period of 3 months.

CONCLUSION

Nanoemulsion used for many applications in pharmacies such as drug delivery systems since their abilities of solubilizing water – insoluble substances. Nanoemulsion possesses many advantages of the delivery drug, Diagnostic, and biological substance. Also it is a protected labile drug, increasing drug solubility, and bioavailability.

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