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NANOEMULSION: A BIOCOMPATIBLE DRUG DELIVERY SYSTEM

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ABSTRACT

Nanoemulsions are identified as a promising delivery system for various drugs including biopharmaceuticals. Nanoemulsions are a type of heterogeneous system composed of one immiscible liquid dispersed as droplets within another liquid. The droplet's size of nanoemulsion is between 20 to 500 nm. Nanoemulsion can be classified as submicron-sized emulsions that act as drug carriers for improving the delivery of therapeutic agents. These are the most advanced nanoparticle systems for the systemic delivery of active pharmaceutical for controlled or sustained drug delivery and targeting. These are thermodynamically stable isotopic systems in which two immiscible liquids (water and oil) are mixed to form a single-phase using appropriate surfactants. Diameter and surface properties of droplets of nanoemulsion play an important role in the biological behavior of the formulation. Small droplet sizes lead to transparent emulsions so that product appearance is not altered by the addition of an oil phase. The nanoemulsion formulations of active ingredients can be used for developing biodegradable coating and packaging films to enhance the quality, functional properties, nutritional value, and shelf life of foods. The future of diagnostics, drug therapies, and biotechnologies are very much dependent upon Nanoemulsion technology.

INTRODUCTION

Nanoemulsion is an isotropic, transparent, heterogeneous system in nature, nanoemulsions are oil-in-water (O/W), water-in-oil (W/O) dispersion of two immiscible liquids consisting of a fine dispersion of drugs in nanodroplets. It is stabilized by an interfacial layer of emulsifiers and co-emulsifiers [1,2]. They are thermodynamically and kinetically stable systems (without any apparent flocculation) with extremely small droplet size (20 to 400 nm), uniform size distribution, and different physicochemical and biological properties than that of other emulsions (>500 nm). The two immiscible phases are usually oil and aqueous in nature which is enriched with the oil and aqueous soluble ingredients, respectively. Mixing oil and aqueous phases forms a coarse emulsion in the presence of emulsifier that may change into nanoemulsion spontaneously or by applying high energy [3, 4]. Nanoemulsions are categorized as a multiphase colloidal dispersion and are characterized by its stability and clarity. The dispersed phase typically comprises small particles or droplets, and they have very low oil/water interfacial tension. Nanoemulsions are thermodynamically metastable as phase separation occurs over time with kinetic stability as there is no gravitational separation and droplet aggregation due to the reduced attractive force between the small-sized droplets. They require fewer amounts of surfactants for their preparation. The droplet size of nanoemulsion

apart from determining its optical property and stability also influences it's rheological and release behavior [5, 6, 7]. As a drug delivery system, they enhance the therapeutic efficacy of the drug and minimize the adverse effects and toxic reactions. Other factors like the capability to undergo direct paracellular/transcellular transport, prolonged gastric retention due to mucosal entanglement, also contribute to nanoemulsion mediated bioavailability enhancement. It has been reported that several nanoemulsions undergo direct lymphatic absorption thereby avoiding the first-pass metabolism to boost bioavailability and reduce the dose of drugs that undergo hepatic transformation to a large extent [8-12].

Factors affecting the formulation of nanoemulsion [13]:

- The surfactant is the most important part of the Nanoemulsion. They should not form lyotropic liquid crystalline "micro-emulsions" phases. Systems containing short chain alkanes, alcohols, water, and surfactants form the phases which are generally used with the co surfactant.
- Appropriate composition is required to avoid Oswald ripening and the dispersed phase should be highly insoluble in the dispersion medium.
- The presence of excess surfactants enables new surface area of nanoscale to be rapidly coated during emulsification there by inhibiting induced coalescence.

Classification of nanoemulsions:

On the basis of composition of oil and water portions nanoemulsion are classified into three types: a) Oil in water (O/W) nanoemulsions in this type the oil droplets are dispersed in continuous aqueous phase b) Water in oil (W/O) nanoemulsions here the water droplets are dispersed in continuous phase which is oil. c) Bi-continuous nanoemulsions are microdomains of oil and water are inter-dispersed within the system. The stabilization of the interface is done by an appropriate combination of surfactants and/or co-surfactants. The O/W nanoemulsions further classified into three types which are as follows:

• Neutral O/W nanoemulsions

• Cationic O/W nanoemulsion

• Anionic O/W nanoemulsions

Advantages of nanoemulsion [14-17]:

1. it gives site-specific delivery of drugs
2. Nanoemulsion has the capacity to dissolve large quantities of hydrophobics
3. Ability to protect drugs from degradation which leads to long term stability which leads to making an ideal drug delivery system
4. This may be used as a substitute for the vesicles and liposomes
5. It is non-irritant and non-toxic
6. This is used to improves the bioavailability of the drug
7. It provides greater absorption because have small-sized droplets having a greater surface area
8. It is possible to formulate it in a variety of formulations i.e., like creams, liquids, foams, and sprays
9. This is also used in taste masking
10. In cell culture technology it provides better uptake of oil-soluble supplements

Mechanism of nanoemulsion system:

The entropy was changed which favor the dispersion is greater than the energy that required to increase the surface of dispersion due to this free energy of conventional emulsion is a direct function of energy is required to create a new surface between oil and water phase and the addition of emulsifying agent to reduce the interfacial tension and because of this emulsion is stabilized [18, 19].

Components of nanoemulsion:

The main components of nanoemulsion are oil, emulsifying agent, and aqueous phase. Oils like oleic acid, ethyl oleate, castor oil, olive oil, clove oil, and Triglycerides. The emulsifying agent or emulgents are added to maintain the stability of such a system. Emulgents are mainly classified as surfactants like Tweens, Spans and Cosurfactant are

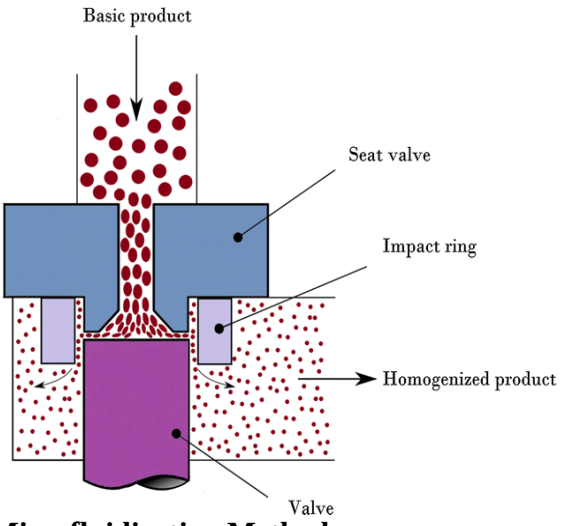
polyethylene glycol 400, polyethylene glycol 200, Polypropylene glycol 400, Ethanol, Propanol, and ethylene glycol has imparted the stability of nanoemulsion. The maximum solubility of drugs and oil in the Emulgents (surfactant and Cosurfactant system) phase is important for the selection of emulsifying agents [20, 21, 22].

DEVELOPMENT OF NANOEMULSION:

The formation of the nanoemulsion system required a high amount of energy of the droplet size range of 100-600 nm, energy can be provided either by mechanical equipment or the chemical potential inherent within the component. The major factor involved in nanoemulsion preparation is to achieve significantly low interfacial tension at the oil/water interface which requires the use of appropriate surfactant. There are divided into two broad categories of techniques for the preparation of nanoemulsions such as high energy methods and low energy methods. High pressure valve homogenization method-Microfluidization method, Ultrasonication method, Phase inversion temperature (PIT), Phase inversion composition method (PIC), Spontaneous emulsification, Solvent evaporation technique/hydrogel method

High Pressure Valve Homogenization Method [23-26]:

The device used in the high-pressure valve homogenization (HPVH) method such as high-pressure valve homogenizers, microfluidizers, and ultrasonicators. High pressure of up to 300 MPa generated in the chamber during delivery stroke causes the coarse emulsion to be pushed out through small orifice of micrometric size by the homogenizer valve. At this stage, the factors such as turbulence, shear stress, and cavitation disrupt coarse emulsions into very finer droplets. The high-pressure homogenization, emulsification occurs in two stages. Firstly, the disruption of the dispersed phase results in tiny droplet formation with increased surface area in the homogenization chamber. In the second stage, the addition of emulsifier molecules undergoes adsorption at interfaces that cause the stabilization of droplets in the chamber. The disruption and stabilization result in the production of a higher number of tiny droplets. An increase in the concentration of emulsifiers in nanoemulsions has also shown to decrease droplet diameter. Studies have shown that small-molecule emulsifiers such as Tween 20 and sodium dodecyl sulfate (SDS), produce smaller droplet sizes than larger molecules emulsifiers such as proteins. High-pressure homogenization cannot be applied for viscous lipids. Thus, high-pressure homogenization efficiently breaks down droplets and increases stability. The applications are, scalability, reproducibility, and high throughput makes high-pressure valve homogenization technique is proceed by using high pressure homogenizer is as shown in figure. 1 [27].



Microfluidization Method:

The basic principle of emulsification by microfluidization is similar to the high-pressure valve homogenizer, having dimensions in the range of 50– 300µm to form droplets in the microfluidization method. A mixing technique, which uses a device called microfluidizer. This device consisting of small channels called microchannels in which Product flows through the microchannels on to an impingement area which results in fine particles of the sub-micron size range. The two solutions such as aqueous phase and oily phase are combined together and processed homogenizer to yield a coarse emulsion. The coarse emulsion is then inserted into a microfluidizer which is further processed to obtain a stable nanoemulsion. The coarse

emulsion is then passed through the interaction chamber microfluidizer repeatedly till the desired particle size is obtained. The bulk emulsion filtered under nitrogen which removes large droplets leading to a uniform nanoemulsion. The premixed emulsion is then circulated through the microfluidizer repeatedly until the required droplet size is achieved [28, 29,]. The process of microfluidization method is processed by microfluidizer based on high shear fluid process is shown in figure.2 [31].

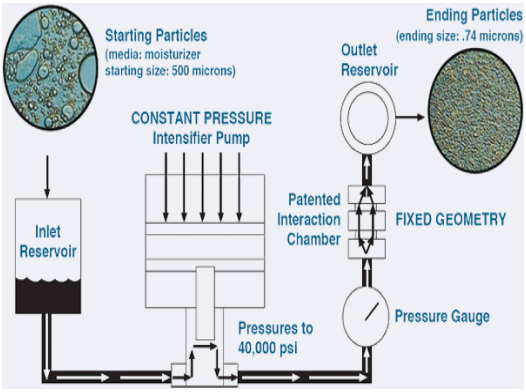


Fig. 2: Microfluidizer high shear fluid process

Ultrasonication Method:

Nanoemulsions can be prepared by using the technique called ultrasonic agitation by sound waves with more than 20 kHz frequency. The ultrasonic sound frequency for reduction of the globule size. the approach is to constant amplitude sonotrode at system pressures in excess of the ambient value. This leads to increasing the external pressure increases the cavitations threshold within an ultrasonic field and thus fewer bubbles form. This means that the collapse of the bubbles when cavitation occurs becomes stronger and more violent than when the pressure is at atmospheric conditions. As cavitation is the most important mechanism of power dissipation in a low-frequency ultrasonic system, these changes in navigational intensity can be related directly to changes in the power density. The system also uses a water jacket to control the temperature to the optimum level. On increasing the sonication time, there is also an increase in input energy which tends to disrupt a higher number of droplets and decrease their size. The other factors which influence nanoemulsion formation are the concentration of emulsifier, viscosity ratio of the dispersed and continuous phase, and the amplitudes of applied waves [32, 33].

Low Energy Methods:

The low-energy methods, use the energy input from the chemical potential of the components from nanoemulsions. The nanoemulsions form spontaneously at the oil and water phase interface by gentle mixing of the components. The spontaneous emulsification can be controlled by two methods. phase inversion temperature and phase inversion composition. These methods involve minimal energy generation and degradation of heat-labile compounds [34].

Phase inversion temperature (PIT):

Methods form nanoemulsions by exploiting changes in aqueous/oil solubility of surfactants in response to temperature fluctuation. It involves ordered the conversion of a W/ O to O/W emulsion or vice versa via a bicontinuous phase. Usually, an oil, water, and surfactant blend are heated past a predetermined temperature, termed as PIT (specific for the utilized formulation blend), and then cooled rapidly. The temperature change from low to high leads to opening and reversal of interfacial structure causing phase inversion. PIT methods may rule out the utilization of thermosensitive drugs. Also, good mutual solubility of water, oil, surfactant, and drug is a prerequisite to facilitate smooth phase transition [35].

Phase Inversion Composition Method (PIC):

In this technique, varying the composition of constituents changes the hydrophilic-lipophilic behavior of emulsifier. On adding salt to an oil-in-water nanoemulsion with an anionic emulsifier, the electric charge of surfactant changes and it turns to a water-in-oil emulsion system. Similarly, a water-in-oil emulsion having high salt content can be converted to oil-in-water by diluting with water [36].

Spontaneous emulsification:

Spontaneous emulsification is a nanoprecipitation method utilized in manufacturing polymeric nanoparticles. The procedure involves the preparation of two phases, one a hydrophilic surfactant-containing aqueous phase and other an organic or oil phases such as miglitol containing a drug, an oil-soluble surfactant such as Span and partial water-miscible organic solvents such as acetone or ethyl acetate. The organic phase is added dropwise to aqueous stirred phase (although the reverse i.e. adding water to oil is equally feasible in case of W/O emulsions) to form small nanoscale emulsions. the low energy method of nanoemulsion formation having the intrinsic physicochemical properties of surfactants and the oily phase plays a major role In the high-energy techniques, the size distribution, and the composition of nanoemulsion [37].

Solvent evaporation technique/hydrogel method:

In this technique, the drug solution is prepared and emulsified into another liquid (non-solvent for drug) and then the solvent is evaporated, which led to drug precipitation. The high-speed stirrer can be employed for regulating the crystal growth and particle aggregation. The hydrogel method is very similar to the solvent evaporation method.

APPLICATION OF NANOEMULSIONS IN DRUG DELIVERY [38-45]:

Nanoemulsion-based delivery systems typically consist of a colloidal dispersion of oil and water phases, with mean droplet diameters typically ranging from about 50 to 500 nm in pharmaceutical applications. Nanoemulsions may exist as an oil-in-water (o/w) or water-in-oil (w/o) form, where the droplets are composed of either oil or water, respectively. Nanoemulsion can be formulated as delivery systems for the administration of drugs through various routes, including oral, parenteral, transdermal, gene delivery, and ocular routes.

Parenteral Delivery: For drugs with low bioavailability and narrow therapeutic index, the parenteral route is considered to be one of the most common and effective routes. The biocompatibility of the raw materials used for their production (oils of natural or semisynthetic origin and phospholipids) makes these systems a promising alternative for the administration of several types of pharmaceutical and nutritional molecules. The composition, structural properties, and preparation conditions of parenteral nanoemulsions should be strictly controlled, aiming at the parenteral administration and the stability of the system. The stability of nanoemulsions for parenteral delivery mainly depends upon their compositions, preparation techniques, and storage conditions. The lipophilic drug candidates delivered as nanoemulsions, after parenteral administration, show a higher plasma concentration compared with the solution form. Moreover, an increase in the volume of distribution and reduction of the clearance leads to an increase in the half-life.

Oral Delivery:

Nanoemulsion formulations over conventional oral formulation show increased absorption, improved clinical potency, and decreased drug toxicity. Nanoemulsion proves to be ideal in delivering drugs such as steroids, hormones, diuretics, and antibiotics. peptides and proteins are highly potent and specific in their physiological functions. Many approaches have been put forth to increase the overall bioavailability of drugs, including micronization/ nanonization, solid dispersions, complexation with cyclodextrins, amorphization, and utilization of particulate delivery systems that are dispersible in aqueous environments.

Topical Delivery: The topical administration of drugs shows in the avoidance of hepatic first-pass metabolism of the drug and related toxicity effects. It also helps in the direct delivery and targeting of the drug to the affected area of the skin or eyes. The nanoemulsion can achieve a high level of topical antimicrobial activity that has only been previously achieved by systemic antibiotics. The nanoemulsion has broad-spectrum activity. For improved drug

pharmacokinetics and targeting, the primary skin barriers need to be overcome. The utilization of delivery systems containing nanosized particles has been highly successful in overcoming this barrier. Nanoemulsion droplets can easily penetrate through the pores of the skin and reach the systemic circulation, thus getting channelized for effective delivery.

Ocular Delivery:

Nanoemulsions are potent drug delivery vehicles for ophthalmic, less than 20% of the applied topical dose that remains in the ocular cavity is increase enzyme binding and metabolism, ocular permeation barriers, phagocytic activity, partial distribution to adjacent tissues, and systemic circulation. The advantages are sustained effect and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor. Cationic nanoemulsions having more bioadhesive properties and more efficient in delivering appropriate concentrations of bioactive molecules in the ocular formulation. The mechanism underlying the bioadhesives of these nanoemulsions is an electrostatic the interaction that prolongs the residence time of the small oil droplets on the ocular surface.

Nanoemulsions for gene delivery:

Nanoemulsion systems delivered genes more efficiently than liposomes. Nanoemulsions with the help of lipid anchors on the oil/water interface conferring a positive charge to them. liposomes can easily bind to the cell surface, they have been used as nonviral vectors for gene delivery such as cationic nanoemulsion. In the presence of cationic surfactants allows the nano complex formation occurs between DNA compaction and has been used to intranasally deliver to protect against neuroinflammation.

CONCLUSION:

In this chapter, the concept of nanoemulsions was discussed such as components, classification, advantages, and factors. Various formulation methods are involved such as high and low energy methods for the development of nanoemulsions. They have a wide range of applications in pharmaceutical systems. It offers several advantages like the delivery of drugs, biological or diagnostic agents. One of the important applications of nanoemulsion is for masking the disagreeable taste of oily liquids. Nanoemulsion protects the drugs, which are susceptible to hydrolysis and oxidation. Recently nanoemulsions are used for targeted drug delivery of various anticancer drugs, photosensitizers, or therapeutic agents. Nanoemulsion provides prolonged action of the medicaments. Maximum all nanoemulsion formulation is considered to be effective, safe, and with increased bioavailability. Further research and development iiscarried out in the future regarding nanoemulsion many more other uses can be discovered.

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