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Review Article

NANOEMULSIONS: A PHARMACEUTICAL REVIEW

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Abstract

Nanoemulsions are submicron sized emulsion that is under extensive investigation as drug carriers for improving the delivery of therapeutic agents. Nanoemulsion as a part of multiphase colloidal dispersion, is a heterogeneous system composed of fine oil in water or water in oil dispersion with surfactant and co-surfactant having droplets covering the size range of 20-600 nm and show narrow size distribution. These are prepared using high energy emulsification method including microfluidic and ultrasonic methods, which rupture large micro droplets into nanoscale droplets provides useful non equilibrium system of structured liquids. Thus the aim of this review is focused on nano emulison advantage and disadvantage, various methods of preparation, characterization techniques and the various applications of sub micron size emulsion in different areas such as various route of administration, in chemotherapy, in cosmetic, etc.

Keywords: Nanoemulsion, Submicron size droplet, Self emulsifying agent, drug delivery.

Introduction

The design of an effective formulation for drugs is major challenge, because of various gastrointestinal side effects, poor solubility, low bioavailability and also instability. The older products can be revitalized by employing novel formulations and delivery systems. New drug delivery technologies can bring new life to older systems by achieving the same efficacy, less side effects, good solubility and bioavailability and enhanced safety. One relatively new means of enhancing delivery is employment of therapeutic Nanoemulsions during discovery and formulation development. Nanoemulsions are kinetically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having the droplet size less than 100 nm.

Solè et. al. (2006) defines nanoemulsions as emulsion systems having particle sizes ranging from 20 - 500 nm. Due to the small droplet sizes, nanoemulsions are believed to be stable against creaming or sedimentation, flocculation and coalescence. However, Tadros, 2005 also stated that nanoemulsions are vulnerable to instability caused by Ostwald ripening. They possess many appealing biological and pharmaceutical properties such as biodegradability, biocompatibility, physical stability and ease of production.

Advantages

1.Nanoemulsions have a much higher surface area and free energy than macroemulsions that make them an effective transport system.

2.Nanoemulsions do not show the problems of inherent creaming, flocculation, coalescence and sedimentation, which are commonly associated

with macroemulsions.

3.Nanoemulsions can be formulated in variety of formulations such as foams, creams, liquids and sprays.

4.Nanoemulsions are non-toxic; non-irritant hence can be easily applied to skin and mucous membranes.

5.Since nanoemulsions are formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.

6.Nanoemulsions do not damage healthy human and animal cells hence are suitable for human and veterinary therapeutic purposes.

7.Better uptake of oil-soluble supplements in cell cultures. Improve growth and vitality of cultured cells. It allows toxicity studies of oil-soluble drugs in cell cultures.

8.They can increase the solubility of drugs exhibiting poor water solubility through entrapment in the core of the nanoemulsion droplets.

9.Nanoemulsions could enhance the stability of chemically unstable compounds by protecting them from oxidative degradation and degradation by light.

10.Possibilities of controlled drug release and drug targeting, and the incorporation of a great variety of therapeutic actives.

11.Due to their small particle sizes, nanoemulsions are able to penetrate easily through skin layers and enhance skin penetration of incorporated drugs.

12.Another important advantage is the low surfactant concentration. Due to their effectiveness for drug solubilization, nanoemulsions offer an alternative for the administration of poorly water soluble drugs. This leads to improved efficacy and compliance because of reduced side effects.

13.The fluidity nature of the system (at low oil concentrations) as well as the absence of any thickeners may give them a pleasant aesthetic character and skin feel.

14.Nanoemulsions can be applied for delivery of fragrants, which may be incorporated in many personal care products. This could also be applied in perfumes, which are desirable to be formulated alcohol free.

Disadvantages

One problem associated with nanoemulsion is their stability. Although it is generally accepted that these systems could remain stable even by years, however, due to the small droplet size, it has been reported that the Oswald ripening could damage nanoemulsions, causing their application to be limited. Therefore, in most cases, nanoemulsions are required to be prepared shortly before their use.

Applications

Nanoemulsion are of great interest as Pharmaceutical, Drugs, Nutraceuticals, Food products & cosmetics formulation. Nanoemulsions are used as drug delivery system for administration through various routes. Parentral, Oral, Topical, Ocular, Pulmonary, Mucosal, Cosmetic, Transdermal, Controlled & Target drug delivery.

Use of Nanoemulsions in Cosmetics and fancy health care vehicles

Nanoemulsions have recently become increasingly important as potential vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers.

Antimicrobial Nanoemulsions

Antimicrobial nanoemulsions are oil-in-water droplets that range from 200-600 nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The nanoemulsion has a broad spectrum activity against bacteria (e.g., E. coli, Salmonella, S. aureus), enveloped viruses (e.g., HIV, Herpes simplex), fungi (e.g., Candida, Dermatophytes), and spores (e.g., anthrax). The nanoemulsion particles are thermodynamically driven to fuse with lipid-containing organisms. This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on

the pathogen. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death. A unique aspect of the nanoemulsions is their selective toxicity to microbe at concentrations that are non-irritating to skin or mucous membrane.

Nanoemulsions as Mucosal Vaccines (Under Trial)

Nanoemulsions are being used to deliver either recombinant proteins or inactivated organisms to a mucosal surface to produce an immune response. The first applications, an influenza vaccine and an HIV vaccine, can proceed to clinical trials. Initial work in influenza has demonstrated that animals can be protected against influenza after just a single mucosal exposure to the virus mixed with the emulsion. Research has also demonstrated that animals exposed to recombinant gp120 in nanoemulsion on their nasal mucosa develop significant responses to HIV, thus providing a basis to examine the use of this material as an HIV vaccine. Additional research is ongoing to complete the proof of concept in animal trials for other vaccines including Hepatitis B and Anthrax. The University of Michigan has exclusively licensed this technology to NanoBio®.

Nanoemulsion as Non-Toxic Disinfectant Cleaner

A breakthrough nontoxic disinfectant cleaner for use in commercial markets that include healthcare, hospitality, and travel, food processing and military applications has been developed by EnviroSystems. The disinfectant is nonflammable and therefore safe to store most anywhere and also to use in unstable conditions. It is nonoxidizing, nonacidic and nonionic. It won't corrode plastic, metals or acrylic, making the product ideal for use on equipment and instruments. It is environmentally safe hence the costs and health risks associated with hazardous chemical disposal are eliminated. The formulation is a broad-spectrum disinfectant cleaner that can be applied to any hard surface, including equipment, counters, walls, fixtures and floors. One product can now take the place of many, reducing product inventories and saving valuable storage space. Chemical disposal costs can be eliminated, and disinfection and cleaning costs can be reduced. Marketed as EcoTru ™ (EnviroSystems,Inc)

Nanoemulsions in Cell Culture Technology

Cell cultures are used for in vitro assays or to produce biological compounds, such as antibodies or recombinant proteins. To optimize cell growth, the culture medium can be supplemented with a number of defined molecules or with blood serum. Up to now, it has been very difficult to supplement the media with oil-soluble substances that are available to the cells, and only small amounts of these lipophilic compounds could be absorbed by the cells. Nanoemulsions are a new method for the delivery of oil-soluble substances to mammalian cell cultures. The delivery system is based on a nanoemulsion, which is stabilized by phospholipids. These nanoemulsions are transparent and can be passed through 0.1-ìm filters for sterilization. Nanoemulsion droplets are easily taken up by the cells. The encapsulated oil-soluble substances therefore have a high bioavailability to cells in culture.

Nanoemulsion in cancer therapy and in targeted drug delivery

The effects of the formulation and particle composition of gadolinium (Gd)-containing lipid NE (Gd-nanoLE) on the biodistribution of Gd after its intravenous (IV) injection in D1-179 melanoma-bearing hamsters were evaluated for its application in cancer neutron-capture therapy. Biodistribution data revealed that Brij 700 and HCO-60 prolonged the retention of Gd in the blood and enhanced its accumulation in tumors.

Nanoemulsion in the treatment of various other disease conditions

Pharmos' (US-based Company) has developed

the nanoemulsion topical diclofenac cream as a potential treatment for osteoarthritis (OA) pain. A topical application of the nanotechnology has already demonstrated excellent targeted delivery of lipophilic drugs to muscle and joints in animal models. Preclinical data using a paw edema animal model showed enhanced anti-inflammatory activity with NSAIDs encapsulated in nanoemulsion creams compared to commercial formulations. Pharmacokinetic studies using nanoemulsion topical creams containing radiolabeled diclofenac and ketoprofen were performed to assess drug penetration through skin and to determine local tissue (muscle and joint) and plasma levels of drugs following topical administration. Primaquine (PQ) is one of the most widely used antimalarial and is the only available drug till date to combat relapsing form of malaria especially in case of *Plasmodium vivax* and *Plasmodium ovale*.

Application of PQ in higher doses is limited by severe tissue toxicity including hematological and GI-related side effects that are needed to be minimized. Primaquine when incorporated into oral lipid NE having a particle size in the range of 10-200 nm showed effective antimalarial activity against *Plasmodium bergheii* infection in Swiss albino mice at a 25% lower dose level as compared to conventional oral dose. Lipid NE of primaquine exhibited improved oral bioavailability and was taken up preferentially by the liver with drug concentration higher at least by 45% as compared to the plain drug.

Nanoemulsion formulations for improved oral delivery of poorly soluble drugs

NE formulations were developed to enhance oral bioavailability of hydrophobic drugs like paclitaxel, ramipril, celecoxib and ubiquinone.

Nanoemulsions as a vehicle for transdermal delivery

Developed NEs have great potential for transdermal drug delivery of aceclofenac, celecoxib, indomethacin.

Criteria for Selection of Topic

Nanoemulsions-based delivery systems have been proved to be one of the best platforms to enhance the oral bioavailability and biological efficacies (that is, antiinflammation, anticancer, and so on) of different phytochemicals. They are especially appealing to food industry because there are many food-grade lipids and emulsifiers available. They are simpler and easier to prepare compared with other lipid-based delivery. This method is gaining considerable importance since it is easy to carry out at a laboratory scale and does not require any high shear equipments like Homogenizer, Probe sonicator etc, which can lead to thermodynamic instability of system. Moreover, the excipients selected for nanoemulsion formulation were under the GRAS (Generally regarded as safe) category and an attempt was made to use as minimum quantity of surfactant as possible. They have been utilized as carriers for lipophilic drugs, for the stabilisation of compounds susceptible to hydrolysis, for the prevention of drug uptake by infusion sets, and for reduction of irritation or drug toxicity. They are used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. resence of nanosized particles (with a large interfacial area), enhanced delivery characteristics, improved biodistribution and pharmacokinetics make these systems appropriate carriers for site specific drug targeting, especially chemotherapeutic agents. Because of these advantages and applications, we choose to prepare nanoemulsion based dosage form for poorly water soluble drugs like ramipril, celecoxib, indomethacin, aceclofenac and atrovastatin so that we can increase their solubility ultimately bioavailability of drug molecule.

Technology / Methods of Preparation:

Nanoemulsion, being non-equilibrium systems, cannot be formed spontaneously. Consequently, energy input generally from mechanical devices or from the chemical potential of the components, is required.

Nanoemulsion formation by the so-called dispersion or high energy emulsification methods is generally achieved using high shear stirring, high pressure homogenizers and ultrasound generators. Production of nano-emulsions by ‘‘low-energy emulsification” methods like PIT (phase inversion temperature) technique involves transitional inversion induced by changing factors that affect the HLB of the system, such as temperature, electrolyte concentration, etc., or catastrophic inversion induced by increasing the dispersed phase volume fraction of the high-energy emulsification

High energy emulsification methods

We will consider emulsification methods involving high (mechanical) energy used in the formation of nano-emulsion, that is to say, the use of devices to force the creation of huge interfacial areas. The formation of such nanometric- scaled droplets is governed by directly controllable formulation parameters such as the quantity of energy, amount of surfactant and nature of the components, unlike the low-energy methods, governed by the intrinsic physicochemical properties and behavior of the systems. High-energy methods present natural predispositions to preserve the formation processes of nano-emulsions droplets, against even the slightest potential modifications of the formulation like the addition of monomer, initiator, surfactant, etc. Three main groups of devices are used in the literature: **The rotor/stator devices, Ultrasound generators and High-pressure homogenizers.**

Rotor/stator type apparatuses, such as Omni-mixerpsy® or Ultraturraxpsy®, do not provide a good dispersion in terms of droplet size and monodispersity in comparison with the nano-emulsions generated by the two others kinds of devices (and also with the low energy methods)

Ultrasound: Nanoemulsions generated by sonifiers are generally attributed to a mechanism of cavitation, but are not as yet understood well enough. The ultrasound waves in liquid macroscopic dispersion result in a succession of mechanical depressions and compressions, generating cavitation bubbles, which tend irremediably to implode. Subsequently, this shock provides sufficient energy locally to increase ΔA corresponding to nanometric -scaled droplets.

High-pressure homogenizers, generally **Microfluidizer** or Manton– Gaulin devices, are designed in order to force macro-emulsions to pass through narrow gaps, by imposing high pressures. The fluid accelerates dramatically, reaching in the microchannels of Microfluidizers for instance, a velocity of around 300 m·s−1. As a result, shear, impact and cavitation forces are applied on very small volumes and generate nano-scaled nano-emulsion droplets (closely related to the phenomena involved in the use of sonifiers). 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 into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber of the 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.

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.

Low-energy emulsification methods

Nano emulsification methods, involving only a low quantity of applied energy to generate nanoemulsions. Nanometric- scaled emulsion droplets may be obtained by diverting the intrinsic physicochemical properties of the surfactants, co-surfactants and excipients composing the formulation. Two groups of methods are proposed in the literature and

developed below:

Spontaneous emulsification describes emulsification as a spontaneous phenomenon which uses the rapid diffusion of water-soluble solvent, solubilized first in the organic phase, moving towards the aqueous one when the two phases are mixed. Among the works on spontaneous emulsification, the literature emphasizes the solvent displacement method, also called the Ouzo effect which consists in nanoemulsion formulation due to the specific and very rapid diffusion of an organic solvent (e.g. acetone, ethanol) from the oily phase to the aqueous one. In theory, the spontaneous nano-emulsification process can provide as much oil-in-water as water-in-oil nano-emulsions.

Phase inversion temperature (PIT) method, which uses the specific properties of polyethoxylated surfactants to modify their partitioning coefficient as a function of the temperature, and leads to the creation of bicontinuous systems when the temperature is close to the PIT, broken-up to generate nano-emulsions. (PIT) method is particularly interesting since it is an organic, solvent-free and low-energy method. The latter two experimental conditions are potentially the most suitable for application in the fields of nano-medicine, pharmaceutical sciences and cosmetics, to prevent the drug to be encapsulated from degradation during processing. Likewise, since the process is relatively simple and low-energy consuming, it allows easy industrial scale-up. The PIT concept was introduced in the last decade by Shinoda and Saito using the specific ability of surfactants, usually nonionic, (NS) such as polyethoxylated surfactants, to modify their affinities for water and oil in function of the temperature, and therefore to undergo a phase inversion.

Evaluation Tests

1. Particle size analysis: Droplet size is thought to have an effect on drug absorption, the smaller size, larger the interfacial surface area will be provided for drug absorption, several variables on droplet size including dilution volume, different media, drug concentration (drug loading) and dispersing method. The effect of dilution on droplet size in distilled water is measured by particle size analyzer (Zetasizer) When dilution time 1000 fold, the droplet size seemed to be unchanged, which revealed that the nanoemulsion formed on dilution was as large as 1000 times capable of keeping drug solubilized.

2. Surface charge measurements: Emulsifiers not only act as a mechanical barrier but also through formation of surface charges zeta potential, which can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more negative zeta potential, greater the net charge of droplets and more stable the emulsion is. Zeta potential values lower than -30 mv generally indicate a high degree of physical stability. It should be noted that a comparison of the zeta potential with the particle size results showed in general, that a decrease in a particle sizes of emulsion was accompanied by a decrease in negative surface charge values.

The droplets size and zeta potential are the more representative parameters in the control emulsion stability and measured by Zetasizer.

3. Percentage transmittance studies: Percentage Transmittance of the prepared nanoemulsion formulation is determined spectrophotometrically. The formulation has the highest percentage transmittance or close to 100% indicated that formulation is clear and transparent. One ml of the formulation is diluted 100 times using solvent and analyzed at λ_{max} using solvent as blank.

4. Thermodynamic stability studies:

1. Heating cooling cycle: - Six cycle between refrigerator temperature 4°C & 45°C with storage at each temperature of not less than 48 h is studied. Those formulation which are stable at these temperature, is subjected to centrifugation test.

2. Centrifugation: - Passed formulation is centrifuged at 3500 rpm for 30 min. Those

formulations that do not show any phase separation are taken for freeze thaw stress test.

3. Freeze thaw cycle: - Three freeze thaw cycle between -21°C & 25°C with storage at each temperature for not less than 48 h is done for the formulation. Those formulation which passed thermodynamic stress test, are further taken for dispersibility test for assessing the efficiency of emulsification

5. Transmission electron microscopy: To observe the morphology of the oil droplets in the nanoemulsion, each batch also characterized by TEM using a negative staining technique.

6. Viscosity determination: The viscosity of the formulations is determined as such without dilution using a Brookfield DV III ultra V6.0 RV cone and plate rheometer at 25 ± 0.3.

7. Refractive index: Refractive index is measured by Abbe type refractrometer.

8. Electrical Conductivity Measurement: Electrical conductivity of the samples is measured using a conductivity meter having a cell constant of 0.11 cm-1 at the frequency of 94 Hz. The measurements were performed in triplicate at 25 ± 1 ºC.

9. In vitro drug release / in vitro skin permeation studies: On basis of delivery system choose we will proceed for dissolution studies or skin permeation studies.

10. **Pharmacokinetic studies/In vivo studies:** On basis of delivery system choose we will do animal studies by using specific animal models.

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