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Review Article

EMULSOMES: A NOVEL LIPOSOMAL FORMULATION FOR SUSTAINED DRUG DELIVERY

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Abstract: Today a huge problem of poorly water soluble is faced in the world. Nowadays many methods are there for increasing the solubility, among them lipid technology is the most prominent and recent technology. At present , the available drug delivery system do not behave ideally, but now a days sincere attempts are going on to achieve them through various novel drug delivery system. Vesicular drug delivery system are selected to overcome problems such as poor drug bioavailability ,protect drug from harsh gastric environment and gastric enzymes and it provides an efficient way for delivery of drug to site of injection, hence decreasing the toxicity and also the adverse effect associated with it. Emulsomes are prepared as novel lipoidal vesicular system with internal solid fat core surrounded by Phospholipid bilayer and this acts as a carrier and vehicle of choice for poorly soluble drugs . Emulsomal based formulations of genetic drugs such as plasmids and antisense oligonuclieotides which are used for gene therapy have good systemic utility and are easily available. Recently the technology have been extensively studied in the aim of improving the efficacy of drug release and also to increase the selectivity of the drugs .It has a wide range of therapeutic application in case of parental drug delivery, gene therapy and also oral formulations. This review addresses about the success of emulsomal drug delivery system and special attention has been focused on advantages, disadvantages, structure, composition, method of preparation, application and various aspects related to emulsomal drug delivery.

Keywords: Drug delivery, lipoidal vesicular system , Phospholipid bilayer, prolonged release, emulsomes

INTRODUCTION

In the past few decades considerable attention has been focused on novel drug delivery systems such as liposomes[1].The new drug delivery system should fulfill two prerequisites, that is it should deliver a specific rate directed by the need of the body during the period of treatment. Secondly it must have the ability to channel the drug into the site of action[2]. Emulsomes are vesicular drug delivery system by encapsulating the active medicament in a vesicular structure. This type of system prolongs the existence of drug in systemic circulation and finally reduces toxicity. The conventional drug delivery system is unable to meet these needs[3].

Emulsomes have the characteristics of both liposomes and emulsions, is encapsulate the drug which is water soluble in the aqueous compartment of surrounding phospholipids bilayers. Emulsomal drug delivery is a liquid based drug delivery system. It has a wide range of therapeutic application in case of parental drug delivery, which is purely water soluble. In case of lipophilic drugs ,since it has limited water solubility large quantity of surface active agents and co-solvents has to be used, but it may lead to toxic effects[4]. Emulsomes are distinct from standard oil in water emulsions. The high Phospholipid content of the monolayer of phospholipids that cover the lipid core which is present at the interface thereby stabilizing the emulsion. In addition, one or more envelope of phospholipids or bilayers is formed around the drug particle in many embodiments. The particle size distribution of emulsomes is in the range of 10-250 nm, which is based on differential weight, making them suitable for intravenous administration.Emulsomal formulation exhibit a sufficiently slow drug release profile that is 12-15% after 24 hours. The in-vivo organ distribution studies demonstrated in rat shows better uptake of emulsomal formulations by the liver cells. Further a significantly higher liver concentration was estimated for cationic emulsomes[5].

ADVANTAGES

- It has low systemic absorption, Site specificity and increased drug levels at injured tissues.
- Emulsomes prevent drug form harsh gastric environment because the drug is enclosed in the triglyceride lipid core. As triglycerides cannot be hydrolyzed by gastric pH and gastric enzymes.
- It increases the solubility as well as bioavailability of poorly soluble drugs. They are composed of triglycerides and they form micelles or arranged as lipid bilayers with hydrophilic head facing the water and hydrophobic tails lined up against one another. . This makes Phospholipid most suitable excipients for poorly soluble drugs.
- Emulsomes provide improved pharmacological activity and reduced toxicity.
- Emulsomes solved the issue of administration of high doses of problematic drugs which are previously could not be administered intravenously in the absence of toxic surfactants.
- Emulsomes are economical alternative as compared to other commercial lipid formulation because they reduce the frequency of dosing of drugs.

DISADVANTAGES

- The major disadvantage of standard oil- in- water emulsion is its limited drug loading capacity.

- Even emulsomes are useful for administration of poorly water soluble drug it could not be administered parenterally as it causes undesirable side effects.
- A correspondingly larger oil phase (10-20%) is required to dissolve the drug, if drug encapsulation above 1% is required.
- The high oil content reduces the stability of the emulsion and hence the addition of surfactants and co-solvents are necessary.
- In case of parenteral administration of drug the use of surfactant is limited, due to the detergent properties of most of the detergents.
- Many toxic reactions of surfactants have been reported, as in case of Fungizone® containing sodium deoxycholate.

STRUCTURE OF EMULSOMES

Emulsions are defined as heterogeneous systems of one lipid dispersed in another in the form of droplets usually exceeding in 1 μm in diameter.

Emulsomes has a microscopic lipid assembly with a lipid core in which water insoluble drugs are placed. (Figure I).Emulsomes composed of a hydrophobic core composed of solid fat instead of oils as in case of oil in water emulsions. The core is stabilized by one or more envelopes of phospholipid as in liposomes. The emulsomes contains a phospholipid layer, lipid core, lipid crown, polar core and liposomal crown (which is present on the surface) [6]. Specific combinations of lipids are used for emulsomes by emulsification and other manufacturing technique.

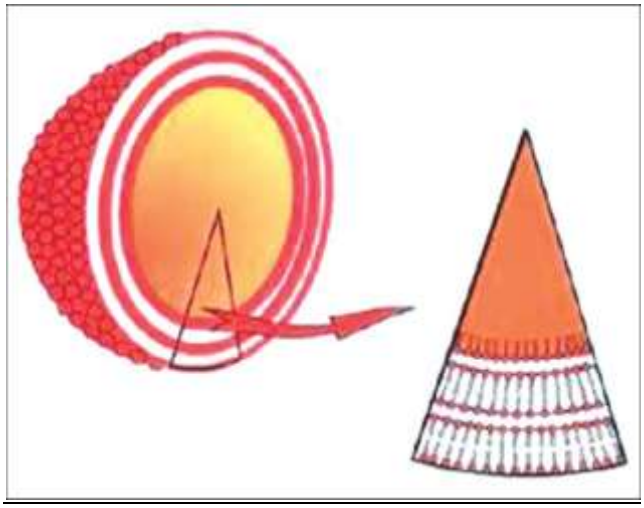

Figure I : Structure of emulsome

PREPARATION OF EMULSOMES

Emulsomes are prepared by mixing triglycerides and phospholipids in the ratio 0.5-1 and it is suspended in aqueous solution, the transition temperature for the preparation is 25°c.By this method a nanoemulsion of particle size 10-250nm is obtained. Then dissolve it in volatile solvents such as dichloromethane and diethyl ether and it is mixed in vacuum to form a lipid film. The formed lipid film is hydrated and an emulsome of size range 140±150nm is obtained (Figure II) [7].

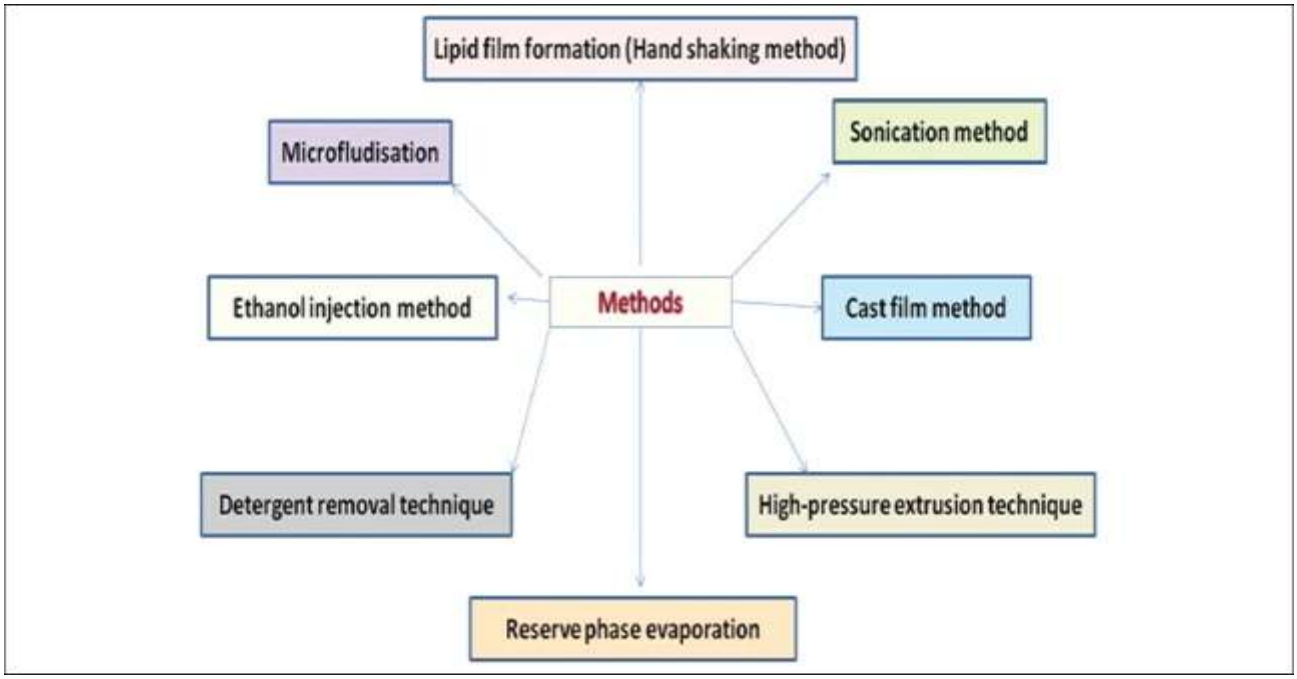

Figure II: Methods of preparation of emulsomes

Lipid film formation (Hand shaking method)

In this method surfactants or lipids are casted as a film in organic solvents using flask rotary evaporator or by hand shaking method. This method is done under reduced pressure and the film is dispersed in aqueous solution or medium. This lipids swells and peel off from the wall of the round bottom flask upon hydration. This is done at a temperature slightly above the transition temperature of the surfactant which is used for specific period of time with constant mild shaking. For dispersion of casted lipid film and the swelling of lipids a mechanical energy is required, which is imparted by and shaking method. Also it can be done by exposing the film to a stream of water; the water is saturated with nitrogen for 15 minutes. And this process is followed by swelling in an aqueous medium which is done wit out shaking. By and shaking method we can produce multi lamellar vesicles(MLV),while non shaking method are used to produce large unilamellar-vesicles(LUV)[8].

Reserve phase evaporation

Reserve phase evaporation is done by two methods, the first method is the preparation of a oil in water emulsion of phospholipids and buffers in excess organic phase. The organic phase is reduced under reduced pressure. The phospholipids and water layer are usually emulsified by sonication(mechanical method).Organic solvents are removed under vacuum cause water droplets which is coated with phospholipids will come together to form a gel-like matrix. Then a paste of smooth consistency was formed by further removal of organic solvent under reduced pressure. This method is useful to achieve 60-65% of drug entrapment efficiency. Both large and small molecules can be encapsulated by this method[9].

High-pressure extrusion technique

When Multi lamellar vesicles are repeatedly passed through very small pore poly carbonate membrane of pore size 0.8-1.0 pm under high pressure, vesicles of minimum average diameter of 60-80 nm is obtained after 5-10 passes. The vesicle become unilamellar when the average size is reduced[10]. This can also be done by using Microfluidizer. It is an instrument in which the feed material is passed through a narrow orifice under high pressure. In case of MLV if it is forced their small orifice, the layers of bilayers are removed from vesicular structure[11].

Sonication method

A solution is prepared by taking different molar ratios of solid lipids, cholesterol & phosphatidylcholine and is dissolved in a minimum quantity of chloroform containing 3 or 4 drops of methanol in a RBF. An accurately weighed amount of drug is added to the previously prepared solution. Under high pressure organic solvent was evaporated until complete dryness is obtained. This is done by using a rotary evaporator to form a thin lipid film on walls of the round bottom flask. The film was hydrated & then homogenize by ultrasonication for 15 min to obtain emulsomes of nano-size range. [12]Phosphate-buffered saline pH 7.4 about 10mL is used to hydrate dried film.

Cast Film Method

In this method emulsomes are prepared by mixing phospholipids and triglycerides in a weight ratio 0.5:1. The prepared mixture is suspended in an aqueous solution at a temperature below solid to liquid transition temperature. The emulsion prepared by this method comprise of a nano emulsion of liquid particles of diameter between 10-250 nm & frequency range within 50-150 nm. The size range of particles is determined in weight % basis rather than particle number basis. The lipid component of this preparation may be volatile & are chemically unreactive organic solvent such as dichloromethane/diethyl ether. Rotary evaporator or stream of inert gas is used to remove solvent under high pressure. By covering & shaking with aqueous solution the formed lipid film can be hydrated & dispersed. If drug is not included in the organic solution, it should be added in aqueous hydration solution.

Ethanol Injection Method

This method is an alternative used to prepare small unilammellar vesicles. In this method, to an excess of saline or other aqueous medium an ethanol solution of surfactant is injected through a fine needle. Vesicles are formed by vapourization of ethanol. A narrow distribution of small liposomes can be obtained by injecting an ethanolic lipid solution in water in a single step without extrusion or sonication. Spontaneous formation of emulsions having a small radius is obtained by this method[13].

Detergent removal technique

In this method a micellar mixture is obtained by mixing phospholipids and detergents, then the detergents is removed from the mixture. Thus the micelles progressively become richer in phospholipids and hence lead to the formation of single bilayers vesicles finally. To remove detergents from preparation methods such as dialysis, column chromatography or absorption onto bio beads are used. The dialysis was previously used for reconstituting biological membrane which is solubilized by detergents. Detergents of high critical micellar concentration were used for the preparation of emulsomes. Sodium cholate, sodium deoxycholate, and octylglycoside are some of the materials used along with other detergents of high CMC in the order of 10-20mM is used in this technique. By this technique homogenous population of single layered emulsomes of 50-100 nm mean diameter is obtained[14].

TYPES OF PREPARATIONS

Emulsomes can be administered in the following forms

- Intranasal
- Oral
- Topical
- Parenteral
- Aerosol
- Inhalation

For parenteral preparation the particle size of emulsome should be in a range 10-250nm.Nano emulsomes are used for ophthalmic preparation which is administered as drops to cornea of eye. Like parenteral preparations, emulsomes for ophthalmic preparations should be sterile and the pH should be close to neutral (6-8)[15].

COMPOSITION OF EMULSOMES

1. Triglycerides:-Lipid cores can be prepared from triglycerides which are used in the preparation of emulsomes. The composition of a triglyceride core can be a single pure triglyceride or mixture of one or more triglyceride(also available as synthetic triglycerides).Fat isolated from natural sources are available as mixture of triglycerides tis is useful in te preparation of emulsomes. The melting characteristics of the mixture is that it act as solid or liquid crystal phase at 250c.The triglycerides used for the preparation of emulsomes are composed of natural, even numbered, unbranched fatty acid of chain length c10-c18 range.[16]

A.Cholesteryl esters:-cholesterol and its esters in high concentration they induce the formation of a liquid crystal phase and it change the packing structure of lipids.

B.Cholesterol monoesters:-Monoesters of fatty acids such as waxes may be the combination of lipids of hydrophobic cores of the emulsomes. Waxes are long chain fatty alcohol esters of fatty acid of melting characteristics for the use of emulsomes, they are solids at 250c.eg: beeswax and spermaceti.

2. Antioxidants:-The lipid core of emulsome may contain one or more antioxidants such as α- tocoperol or its derivatives .One of the most preferred antioxidant is of vitamin E family. Other examples of antioxidants are butylated hyddroxytoluene.(BHT)

3. Protein components:-Serum apolipoproteins such as Apo B , ApoAI, APO AII or Apo E are not present in lipid particles. Apo B protein as the ability to target lipid particles to certain cellular receptor (LDL receptor) in hepatocytes and other cells also by intravenous administration[17].

4. Surface active molecules:-One envelope of the layer containing phospholipid molecules which surround the lipid core. Phospholipid layer act as a stabilizer or surface active agent and this lowers the surface tension. Around the lipid core of the particles a surface active phospholipid layers are believed to form a monolayer with apolar head group at the interface. Lipid cores can be encapsulated by one or more roughly concentric bilayers by using excess phospholipids and the number of bilayer envelope the core varies. This bilayers envelop entrap one or more aqueous components which may contain a water soluble drug. In the structure of emulsome multiple concentric bilayer models are used which accounts for the ability of the particle to carry high load of lipid soluble drugs and water soluble drugs.

5. Surface active agents: - Negatively charged phospholipids such as phosphatidine glycerol or phosphatidic acid and negatively charged lipid molecules such as oleic acid is used to increase the zeta potential of the composition of lipid phase of emulsomes and thus stabilising the particles. Additionally, negatively charged lipid compounds can be incorporated in emulsomes for the formation of phospholipids bilayer with opposing charges. Thus the water soluble molecules in aqueous compartments formed by phospholipid bilayer by increasing the load. Sometimes small amount of detergents and non natural surfactants are incorporated into emulsomes. Wide variety of manmade molecules which forms micelles in aqueous solutions can be used as non natural surfactants or detergents, which contain both hydrophilic and hydrophobic domains. Example: Tweens[18].

MECHANISM OF EMULSOMES ABSORPTION

The structural similarity of emulsomes with chylomicrons which are natural lipoprotein of the body, are accepted to mimic the behavior of lipoprotein. Endogenous lipid absorption mechanism is used for taking up of lipids like particles through enterocytes of gastrointestinal tract.[19] The coordination of synthesis of apolipoprotein and lipids and its intracellular assembly to form mature lipid containing particles are complex incidents involved in the intestinal absorption of long chain triglycerides from enterocytes. Monoglycerides and triglycerides are the digestive products of triglycerides which are absorbed by passive diffusion and transported through the enterocytes to endoplasmic reticulum. The endoplasmic reticulum is the site where the biosynthesis of lipids takes place. Lipoproteins are made in endoplasmic reticulum and transported to golgibodies. Lipid based excipients influence oral absorption by retarded gastric emptying, stimulating bile flow, secretion of pancreatic juice etc.

APPLICATIONS OF EMULSOMES

1. Incorporation of a neuroprotectant drug: - In this method, all lipid components are mixed with dichloromethane and by using a rotary evaporator the organic solvents are evaporated under reduced pressure. 50mL saline is added to dry lipid and by shaking the mixture until the lipids are homogeneously dispersed in aqueous phase. The preparation is subjected to high shear homogenization at 800 bar pressure for 15 cycles using micro lab 70 Gaulin homogenizer. The particle size distribution of formulation is determined by N4MD Coulter particle size analyzer after filtering the formulation trough 0.2 micrometer sterile filter membrane. A homogeneous emulsion of mean particle diameter (153±24nm) was obtained.

2. Incorporation of psycho tropically active agents in emulsomes:- In this method, all lipid components are mixed with dichloromethane and by using a rotary evaporator the organic solvents are evaporated under reduced pressure. 50mL saline is added to dry lipid and by shaking the mixture until the lipids are homogeneously dispersed in aqueous phase. The preparation is subjected to high shear homogenization at 800 bar pressure for 15 cycles using micro lab 70 Gaulin homogenizer. The particle size distribution of formulation is determined by N4MD Coulter particle size analyzer after filtering the formulation trough 0.2 micrometer sterile filter membrane. A homogeneous emulsion of mean particle diameter (153±24nm) was obtained.

3.Antifungal drugs:- Mechanism of action of amphotericin B: The membrane permeability changes by interaction of amphotericin B with membrane sterol and which leads to cellular dysfunction and eventually to cell destruction and death. AmB inhibits membrane enzymes like proton ATPase in fungal cells and sodium/potassium ATPase in mammalian cells. The inhibitory activity depletes cellular energy reserves and hence reduces proliferative ability of the cell. AmB is poorly soluble in water as it is an amphoteric compound composed of a hydrophilic poly hydroxyl chain on one side and a lipophilic polygene hydrocarbon chain on other side. Fungizone is commercially available as a colloidal suspension of amphotericin B in which the bile salt deoxycholate is the solubilising agent.

4. AIDS Drugs: - Zidovudine is an approved drug for treatment of AIDS also known as Azidothymidine (AZT). The solubility in aqueous buffer of AZT-CDS is limited by

lipophilic characteristics of this drug and therefore lipophilic delivery vesicles are needed. The use of organic cosolvents such as DMSO-polyethylene glycol mixture, inclusion in macromolecular complexes like cyclodextrin or incorporation into lipoidal carriers. AZT-CDS is incorporated into emulsomes and hence increased brain levels of AZT were obtained[20].

5. Anti-neoplastic treatment:-In case of Anti-neoplastic treatment it shows severe side effects. Emulsomes can alter the metabolism, prolong circulation and half life of the drug and hence decrease the side effects. Emulsomal entrapment of Methotrexate shows beneficial effects over the unentrapped drugs such as decreased rate of proliferation of the tumor and ig plasma level accompanied by low elimination[21].

CONCLUSION

Emulsomes have characteristics of both liposome and emulsomes, and have high loading capacity of poorly aqueous soluble drugs in its internal lipid core, also have the ability to entrap water soluble drugs with varied bioavailability. Emulsomes increase the effective luminal solubility of drugs and also can be used for drug targeting to recticulo-endothelial system. Emulsomal formulation sow a small drug release profile of about 12-14% after 24 hours emulsomes play a major role in parenteral drug delivery of purely water soluble. As emulsomes are of nano range as compared to niosomes, pharmacosomes and ethosomes they are more effective in improving the bioavailability. Emulsomes are also a best carrier for intravenous as well as oral delivery of drug.

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