



GLOBAL JOURNAL OF MEDICAL RESEARCH: B
PHARMA, DRUG DISCOVERY, TOXICOLOGY & MEDICINE
Volume 22 Issue 2 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Review on Emulsomes as Carriers for Drug Delivery

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GJMR-B Classification: DDC Code: 610.3 LCC Code: R121



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Review on Emulsomes as Carriers for Drug Delivery

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Abstract- This review determines the introduction to emulsomes, need to the invention, advantages, disadvantages, formulation of the emulsomes, methods of preparation and application of emulsomes. In the recent years attention has been focused on development of vesicular drug delivery system. These emulsomes provide the drug release in a controlled and sustained manner up to 24 hours, whereas the liposomes have shown release up to the mark of 6 hours. Emulsomes comes under the category of the vesicular drug delivery system and these are mainly developed for the purpose to overcome poor bioavailability, protection from harsh gastric environment and from gastric enzymes, which mainly degrade the drug molecules. The success of the emulsomes is for the delivery of drugs to fight against viral infections, fungal infections, dermal therapy, cancer, auto immunity. Mainly the drug is enclosed in the emulsomes and provide existence of drug in systemic circulation. Emulsomal based formulations of genetic drugs, antisense oligonucleotides and plasmids for gene therapy having proper and clear potential for systemic utility are increasingly available. The worldwide market for drug delivery systems is growing at an ever-increasing rate and is being fueled by several significant needs, the commercial necessity of extending product life and product portfolios, the clinical need to enhance drug safety and patient compliance and the technological challenge of delivering new therapeutics. Exploitation of new advances in drug delivery technology will give pharmaceutical companies a significant competitive advantage in an increasingly demanding marketplace.

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1. INTRODUCTION

a) Emulsomes

Emulsomes are nanosize in range compared with the other vesicular drug delivery system such as niosomes, pharmacosomes, ethosomes. Due to their reduced size, they can be used to increase the bioavailability of drug and as the best carrier for the intravenous delivery as well as the oral drug delivery[1]. Oral route is the best route to reduce the number of adverse effects. Emulsomes are novel oral drug delivery systems which carries lipophilic drugs within it. Emulsomes are lipoidal vesicles which contains solid fat

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core surrounded by phospholipid bilayer. They are the liposomes with extra single inner phospholipid layer which contains solid fat. The drug release pattern by emulsomes is sustained and slow release and it is also soluble in aqueous phases and can be easily circulated through blood[2]. The Emulsome nanocarrier technology is a lipid-based drug delivery system designed to act as a vehicle for drugs with poor water solubility. Emulsome particles consist of a microscopic lipid assembly with an internal fat core, which dissolve the water-insoluble drugs in the absence of any surfactant or solvent.

b) Need for the invention

Undesirable side-effects are often produced when water-insoluble vehicles are used for the parenteral administration for example thrombophlebitis, hemolysis, or blood coagulation. The potential carriers for fat soluble materials are liposomes and o/w emulsions which minimize such undesirable side effects. However, there are many problems with stability and drug loading capacity which have been reported using either of these delivery systems[3].

c) Liposomes

It consists of one or more concentric phospholipid bilayers, separated by water or aqueous compartments, range from 20nm to 10 μ m.

They are

1. SUV (20-100nm)
2. LUV (> 100nm)
3. REV (0.5 μ m)
4. MLV (2-10 μ m)

Effective for localized sustained release of drugs in tissues [4].

Drawbacks of liposomes

1. Unilamellar Vesicles- low content of lipid molecules so
 - Low drug loading capacity for lipophilic compounds
 - More suitable for entrapment of water –soluble materials
2. Amount of drug that can be contained therein is limited.
3. MLV liposomes- not appropriate for I.V due to large size.
4. Difficulties in preparation of acceptable liposomal formulations with long-term stability and high drug loading [2].

d) *Emulsions*

Emulsions are defined as “heterogeneous systems of one liquid dispersed in another liquid in the form of droplets usually exceeding 1 μm in diameter”. The two liquids are immiscible and are chemically not reactive or slowly reactive. An emulsion is a thermodynamically unstable dispersed system. This instability causes reduction in its free energy by separating the dispersed droplets into two liquid phases.

Evidenced of emulsion instability during storage:

- Creaming
- Flocculation
- Coalescence [5]

Drawbacks

1. Micro-droplets of size less than 1 μm should be achieved to prevent the formation of emboli in blood vessels.
2. Emulsifiers must be coated to lower the free energy at the interface and decrease the tendency of droplets to coalesce. These emulsifiers produce harmful side effects upon injection into the body.
3. It has detergent characteristics because most of them are hemolytic agents which act as membrane solubilizers.
4. Limited formulation options due to restricted emulsifiers for safe parenteral injection.
5. The water insoluble drugs such as phenytoin, amphotericin B, cyclosporin, miconazole, diazepam, etoposide, etc makes the formulation difficult for intravenous use.
6. These drugs are marketed in co-solvent systems such as polyethylene glycol or propylene glycol-ethanol-benzyl alcohol mixtures, which have shown toxicity problems, such as thrombophlebitis on injection.
7. Alternatives to cosolvent systems are micellar solutions or emulsions, but the presence of toxic surfactants in these systems makes them undesirable for intravenous administration[5].

Summary of the invention

To provide pharmaceutical compositions comprising nano-emulsions of particles comprising of lipid core composed of lipid which is in a solid or liquid crystalline phase atleast 25° C, stabilized by at least one phospholipid envelope, for parenteral, oral, rectal, intranasal or topical delivery of both fat-soluble and water-soluble drugs.

This is solid fat nanoemulsion or “EMULSOMES”.

Emulsomes, having the characteristics of both liposomes and emulsions [1]

II. FORMULATION

1. Composition of lipid core

It exhibits solid (or) liquid crystal or mixed solid and liquid crystal phases at room temperature (25°C) when measured in bulk. Lipid compositions suitable for use as the core component of emulsomes may be characterized as being in the solid or liquid crystalline phase at least about 25°C., when measured in bulk form without incorporation into emulsomes. Some lipid compounds present in a mixture optionally may be fluids at 25°C. When pure provided that the lipid mixture as a whole is solid or liquid crystalline in bulk at 25°C. In preferred compositions, at least 90% of the individual lipid compounds present in the core are solids or liquid crystals at 25°C when measured in pure bulk form.

Phase determination is performed on the bulk lipid, incorporation into the emulsome core. The macroscopic phase determination on a bulk sample may be made on a melting apparatus or by spectroscopic means, such as IR, NMR, or fluorescence intensity or anisotropy. Bulk phase determination of an existing emulsome preparation may be performed by first extracting the core lipids, then measuring.

It consists of - triglycerides,

- Monoesters,
- Cholesterylesters & cholesterol,
- Antioxidants,
- Protein components [6]

a) *Triglycerides*

Available as synthetic triglycerides or mixture of several triglycerides. Fats isolated from natural sources usually are available only as mixtures of triglycerides. Such natural mixtures are suitable for preparation of emulsomes, provided that the melting characteristics of the mixture are such that they exhibit a solid or liquid crystal phase at 25°C.

Triglycerides, which are solid at 25°C have fully saturated fatty acid chains which are incapable of undergoing peroxidation reactions.

Examples of solid fats suitable for the preparation of emulsomes are:

Triglycerides composed of natural, even-numbered and unbranched fatty acids with chain lengths in the C10-C18 range, or microcrystalline glycerol triesters of saturated, even-numbered and unbranched fatty acids of natural origin such as tricaprin, trilaurin, trimyristin, tripalmitin, and tristearin.

Partially hydrogenated vegetable oils may be used to prepare emulsomes which are free of cholesterol or cholesteryl esters [7].

In some the lipid of the hydrophobic core may have a solid to fluid phase transition (melting) temperature between 25°C and physiological temperature (37°C) when measured in bulk. For example, tricaprin melts at 35°C-37°C., and is wholly or

predominantly in the fluid phase at physiological temperature. Tricaprin may be used to form an excellent lipid core for nanoemulsions. Lipid core may be composed of lipid, which is in solid phase at 37 °C.

Ex: higher saturated triglycerides-tripalmitin and tristearin

b) Monoesters

The lipid core may contain monoesters of fatty acids such as waxes

Ex: Esters from beeswax and spermaceti-cetyl palmitate

Preferred waxes are made from saturated or monounsaturated fatty acids and saturated or unsaturated fatty alcohols.

Ex: Arachidyl oleate

Other monoesters include solid monoglycerides such as glyceryl monostearate, and fatty acid esters of short chain alcohols such as ethyl stearate [8].

c) Cholesteryl esters & cholesterol

These can be incorporated into the lipid core or the surrounding phospholipid envelope. cholesterol has a polar alcohol group, it tends to incorporate into the envelope monolayers or bilayers rather than into the lipid core itself, and should be considered a component of the phospholipid envelope rather than of the core [9].

Preferred cholesteryl esters are those of saturated or monounsaturated long chain fatty acids, such as palmitoyl or oleoyl, respectively.

Cholesteryl esters may be present in levels up to 50 mol % relative to the triglyceride or other solid lipid core component [10].

d) Antioxidants

Lipid core may contain one or more antioxidants.

The need for antioxidants may be lessened by preparing the lipid core from saturated fatty acids.

Ex: Alpha tocopherol & its derivative
Butylated hydroxytoluene

e) Protein components

Lipid particles of the invention preferably do not contain serum apolipoproteins such as apo B, apo AI, apo AII, or apo E.

The apo B protein has the effect of targeting intravenously administered lipid particles to certain cellular receptors, such as the LDL receptor on hepatocytes and certain other cells.

Other proteins and peptides optionally may be present in emulsomes.

Examples of such peptides and proteins may be cyclosporin, luteinizing hormone releasing hormone (LHRH) and its analogs, calcitonin, insulin, and other synthetic or recombinant peptides.

An example of natural protein is collagen, which may be used to prepare emulsomes with controlled or sustained release properties.

2. Phospholipids: Constitute the surrounding envelope of emulsomes

Ex: 1. Natural phospholipids - soybean lecithin, egg lecithin, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidic acid, diphosphatidylglycerol, Cardiolipin, phosphatidylserine, phosphatidylcholine, sphingomyelin.

2. Synthetic phospholipids- dimyristoyl & distearoyl phosphatidylglycerol, dimyristoyl & dipalmitoyl phosphatidylcholine, Hydrogenated lecithin & phospholipids.

The phospholipid component may be either saturated or unsaturated, and may have a gel to fluid phase transition temperature either above or below 25°C.

Ex: egg or soy PC – below room temp
dimyristoyl PC – slightly below room temp
distearoyl & dipalmitoyl PC –above room temperature
emulsomes prepared with phospholipids which are in the gel phase at 37°C are expected to have more rigid bilayer envelopes and longer circulation time in plasma.

Emulsomes may be prepared with molar ratios of phospholipid to total lipid in the range of 0.1 to 0.75 (10 to 75 mol %), more usually 0.1 to 0.5 (10 to 50 mol %). The molar ratio of phospholipid to core lipid typically may be in the range of 0.1:1 to 2:1, usually 0.1:1 to 1:1, often 0.2:1 to 0.9:1, frequently 0.2:1 to 0.8:1, and commonly 0.25:1 to 0.6:1.

On a weight basis, the ratio of phospholipid to core lipid usually falls in the range 0.5:1 to 1.5:1, and frequently 0.6:1 to 1.2:1. [1]

3. Non-natural surfactants: optionally may be incorporated into emulsomes in small amount as less than 0.1% to less than 10% (mol/mol) of total surfactants.

The increasing concentrations of synthetic surfactants progressively decrease the particle size, and higher concentrations than those used are expected to result in formation of micelles (1-10 nm diameter).

4. Negatively charged lipids: These are added to the lipid phase of emulsomes to increase the zeta potential of the composition, thus stabilizing the particles.

Incorporation of these negatively charged lipid compounds in emulsomes results in the formation of phospholipid bilayers with opposing charges, thus increasing the loading of water-soluble molecules in the aqueous compartments formed by the phospholipid bilayers surrounding the lipid core.

Inclusion of negatively charged lipid molecules in emulsomes is to reduce the likelihood of particle aggregation, which minimizes destabilizing processes such as coalescence, flocculation, or fusion. Aggregation is prevented by the repulsive forces between the approaching particles.



Ex: negatively charged lipid molecule-oleic acid negatively charged phospholipid- phosphatidylglycerol, phosphatidic acid, phosphatidylserine, phosphate-dylinositol

Range is 0 to 30-mol % relative to total phospholipid & charged lipid.

5. Incorporation of drugs

Water insoluble compounds – incorporated by dissolving drug in suitable organic solvent along with other ingredients.

Water-soluble drugs- by dissolving in aqueous medium.

Categories of drugs incorporated

Antifungal, antiepileptic & anticonvulsant drugs, beta-adrenergic blockers, aids drugs, anti-anxiety agents, anti-depressants, corticosteroids, anabolic steroids, estrogens & progesterones. [11]

III. PHARMACEUTICAL PREPARATIONS OF EMULSOMES

a) Method

1) Lipid film formation (Handshaking method)

Surfactants/lipids are casted as layers of film on their organic solution using flask rotary evaporator under reduce pressure (or) by hand shaking. The casted films are dispersed in aqueous. Hydration is done with constant hand shaking. The lipids will swell and get peeled off from the walls of round bottom flask at slightly above the phase transition temperature of surfactants used for specific period of time. Swelling of lipid and dispersion of casted lipid film is done by manual hand shaking or by exposing the film to a steam of water saturated nitrogen for 15 minutes, followed by swelling in the aqueous medium without shaking. Hand shaking method produce multi lamellar vesicles (MLV) and non-shaking method produced large unilamellar vesicles (LUVs).

2) Reserve phase evaporation

This technique is comprised of two steps. First prepare a water-in-oil emulsion of phospholipids and buffer in excess organic phase. Second remove organic phase under reduced pressure. The two phases of phospholipids and water are usually emulsified by mechanical methods. Remove the organic solvent under vacuum, it causes the phospholipid coated water droplets to combine to form a gel-like matrix. Further continual removal of organic solvent under reduced pressure causes the gel like matrix to form into a paste of smooth consistency, which is a suspension of LUV. Drug entrapment efficiency is achieved up to 60-65%. This method is used to encapsulate both small and large molecules. Avoid the exposure of drug to be encapsulated to organic solvents and to mechanical agitation as less as possible. Phospholipids are dissolved in organic solvents such as chloroform, isopropylether, or mix two organic solvents to adjust the

density to unity that is closer to the density of aqueous phase. Biologically active molecules such as enzymes, protein pharmaceuticals and RNA type molecules may undergo conformational changes, protein denaturation, or breakage of DNA strands due to the harsh conditions of organic solvent exposure and mechanical agitation[7].

3) Ethanol injection method

It is the alternative method used for the preparation of small unilamellar vesicles (SUVs). An ethanol solution of surfactant is injected rapidly through a fine needle into excess of saline or other aqueous medium. Vaporize the ethanol for the formation of vesicles. Narrow distribution of small liposomes (under 100 nm) can be obtained by simply injecting an ethanolic lipid solution in water, i.e. in one step, without extrusion or sonication. This method is a suitable technique to obtain the spontaneous formation of emulsomes with small average radius. Alternatively, the lipid or lipid mixture is dissolved in alcoholic solvent and an aliquot of 200, 500, or 600 ml fast injected at room temperature, 1 ml syringe into the dispersant solution, which contains water or saline solution, of 9.8 ml further diluted to 1:50, 9.5 ml diluted to 1:20 or 9.8 ml diluted to 1:17, respectively. The solution was then vigorously hand-shaken for 20-30 seconds. After that the ethanol solution is fast-injected in a 5% glucose solution. The vesicles had shown average diameter of about 60 nm and may be stable for at least one week[6].

4) Cast film method

Mix the phospholipids and triglycerides in a weight ratio of 0.5:1.0 where triglycerides have a solid to liquid phase transition temperature of greater than 25°C. Suspend the mixture in an aqueous solution at a temperature below the solid to liquid transition temperature in order to reduce the suspension to yield emulsomes. These emulsomes comprise a nano-emulsion of liquid particles having a mean particle diameter between 10-250 nm usually within the range 20 to 180 nm usually and frequency within range 50-150 nm. The size range is determined on a weight percentage basis rather than a particle number basis. Usually, the lipid component may be volatile and chemically un-reactive volatile organic solvent such as dichloromethane or diethylether. Remove the solvent under reduced pressure in a rotary evaporator or under stream of inert gas. The resulting lipid film is then hydrated and dispersed by covering and shaking with an aqueous solution. If the drug component were not included in the organic solution, they may be added to aqueous hydration solution. Size the lipid suspension or dispersion at 800 pressure bars by high shear homogenizer.

5) Detergent removal technique

Phospholipids and a detergent are mixed together to form micellar mixtures. The detergent is

removed from the preparation while the micelles progressively become richer in phospholipid content and the lipids come together to form single bilayer vesicles. Methods such as column chromatography, dialysis or adsorption onto bio beads used to remove the detergent from the preparation. The dialysis technique was first reported for reconstituting biological membranes solubilized with detergents. This method is also applicable for the preparation of emulsomes. Commonly used detergents here are those with high critical micelle concentration. Ex: sodium cholate, sodium deoxycholate, and octylglycoside. In this technique detergent is removed by a flow through dialysis cell from phospholipid detergent mixture. Reports were found that this technique yielded homogeneous population of single layered emulsomes with mean diameters of 50-100nm[4].

APPLICATIONS OF EMULSOMES

1. Entrapment of water insoluble drugs
 - Neuroprotectant drug HU-211
2. Encapsulation of water –soluble drugs
 - Adaprolol- Maleate
3. For controlled release
4. As blood substitutes or oxygen carriers
 - Stable blood–substitute perfluorodecaline formulation
 - Perfluorotributylamine formulation
5. Can be lyophilized
6. In anti-viral therapy (anti HIV)
 - AZT- CDS in emulsomes
 - Brain enhanced delivery of AZT-Q by AZT-CDS-emulsomes
7. For ophthalmic use
 - 1% Indomethacin
8. For topical use as creams
 - 1% Indomethacin
 - Diclofenac & ketoprofen
9. In anti-fungal therapy
 - Miconazole
 - Amphotericin-B
10. Antiepileptic & anticonvulsant
 - Diazepam
 - Phenytoin
11. For sustained & targeted delivery
 - Zidovudine – to liver
12. For immunization
 - HIV-1 neutralising antibodies in genital & respiratory tracts of mice intranasally immunized with oligomeric gp160 formulated in emulsome[3]

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