REVIEW ARTICLE

Emulsomes: An emerging vesicular drug delivery system

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The oral route is the easiest, cost effective, and most vital method for drug administration. Therefore, improvement of dosage forms mainly for the prolonged release purpose has been a challenge for scientists. Vesicular drug delivery systems are developed with a purpose to overcome problems coupled with the drugs such a poor bioavailability, protection from harsh gastric environment, and from gastric enzymes, which degrade the drug. Vesicular drug delivery systems such as liposomes, emulsions, niosomes, proniosomes, solid lipid-nano particles, ethosomes, nanoparticles, and pharmacosomes, etc have gained much attention, but emulsomes have rouse as system, which bypasses many disadvantages associated with other systems, developed as novel lipoidal vesicular system with internal solid fat core surrounded by phospholipid bilayer. This technology is designed to act as vehicle for poorly soluble drugs. The drug is enclosed in the emulsomes and provide prolong existence of drug in systemic circulation. Furthermore, emulsomal-based formulations of genetic drugs such as antisense oligonucleotides and plasmids for gene therapy that have clear potential for systemic utility are increasingly available. This review addresses the concept of emulsomal drug delivery system, summarizes the success of emulsomes for the delivery of small molecules, and special attention has been paid to its formulation design, advantages, biopharmaceutical aspects, stability aspects, and various aspects related to drug delivery including future aspects.

Key words: *Controlled oral drug delivery, emulsomes, oral bioavailability, vesicular drug delivery*

INTRODUCTION

In past few decades attention has been focused on development of vesicular drug delivery system. Nowadays, vesicles as a carrier system have become the vesicles of choice in drug delivery and lipid vesicles are established to be valuable in immunology, membrane biology, and diagnostic technique, an d most importantly in genetic engineering. Lipids are referred to a group of naturally occurring molecules which include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), as well as mono-glycerides, triglycerides, phospholipids. Lipids may be broadly defined as hydrophobic or amphiphilic small molecules; the amphiphilic nature of some lipids allows them to form structures such as that of vesicles.[1] Therefore, researchers recognize the potential of the lipids for delivering soluble materials for extended periods.[2] Vesicles are unilamellar or multilamellar spheroid structures composed of lipid molecules assembled into bilayers, Because of their capacity to carry a number of drugs, vesicular delivery systems have been widely investigated for their prospective application in pharmaceutics such as drug delivery[3-5] for drug targeting,[6] for controlled release,[7] or for increasing solubility.[8]

Emulsomes is a novel lipoidal vesicular system with an internal solid fat core surrounded by a phospholipid bilayer. Structure of emulsomes is shown in Figure 1. Emulsomal formulations composed of solid lipid core material and stabilized by cholesterol and soya lecithin. The drug is loaded followed by sonication to produce emulsomes of small size.[9] The polymer used for core material should be solid at room temperature (25°C).[10] The high soya lecithin concentration stabilized the emulsomes in form of O/W emulsion.[11] These fat cored lipid particles are dispersed in an aqueous phase. These systems are often prepared by melt expression or emulsion solvent diffusive extraction.

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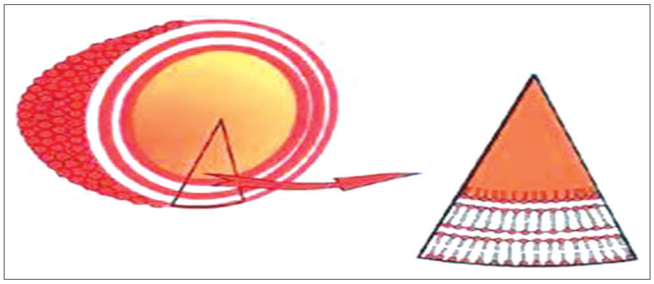

Figure 1: Structure of emulsome

Emulsome represents lipid-based drug delivery systems with broad variety of therapeutic applications particularly for drugs that are poor aqueous soluble.[12] Emulsomes consist of microscopic lipid assembly with a polar core, which contains water insoluble drugs in the solution form without requiring any surface active agent or co-solvent. Beside the other vesicular formulations, emulsomes are much stabilized and nano range vesicles. It is a new emerging delivery system and therefore could play a fundamental function in the effective treatment of life-threatening viral infections and fungal infections such as hepatitis, HIV, Epstein-Barr virus, leishmaniasis, etc. appear promising for the treatment of visceral leishmaniasis specifically and hepato-splenic candidiasis.[9-11] Furthermore, in systemic fungal infections, the systems can be used for rapid loading of reticuloendothelial system organs with the incorporated drug for the complete eradication of the intracellular pathogens. Emulsomes could be utilized in order to improve oral controlled delivery of drug, vaccine, and bioamcromolecules. It is due to the fact that they are nano sized in range and could be utilized for the intravenous route. Moreover, emulsomes could represent a more economical alternative to current commercial lipid formulations for the treatment of viral infections and fungal infections. Emulsomes provide a controlled and sustain release of drug. In comparison to the liposomes, emulsomes provide a prolong release of drug upto 24 hours, whereas liposomes have shown release upto 6 hours.[12-14] Emulsomes are nano size range in comparison to other vesicular delivery system such as niosomes, pharmacosomes, and ethosomes. Due to the reduced size they can be used to enhance bioavailability to drug and as the best carrier for the intravenous drug delivery as well as oral drug delivery.

Advantages of emulsomes

Emulsomes defend drug from harsh gastric environment of stomach before oral administration because the drug is enclosed in the triglyceride lipid core. This hypothesis could be supported by the fact that gastric pH and gastric enzymes are unable to hydrolyze triglycerides.

Emulsomes increase the solubility and bioavailability of poorly aqueous soluble drugs. They are composed of triglycerides and form micelles or are organized as lipid bilayers with the hydrophobic tails lined up against one another and the hydrophilic head-group facing the water on both sides. These unique features make phospholipids most suitable to be used as excipients for poorly water soluble drugs.

Emulsomes are composed of lipid core. Lipids are used to develop oral controlled delivery of drug. The wide spread adoption of lipid based strategies for enhancing drug exposure is limited.

Emulsomes are economical alternative to current commercial lipid formulations because they reduce the dosing frequency of drug.

Emulsomes-based system showed excellent potential for targeting. The formulations could significantly modify providing prolonged action at comparatively low drug doses thereby reduction in the toxicity problem due to complimentary localization of the drug in target cells.

They provide significantly modify the pharmacokinetics of drugs.

Also, they resist development of multi drug resistance, often associated with over expression of a cell membrane glycoprotein, which cause efflux of the drug from the cytoplasm and results in an ineffective drug concentration inside the cellular compartment.

Mechanism of emulsomes absorption

Emulsomes have structural similarity with the chylomicrons (natural lipoprotein of the body) and consequently expected to mimic these lipoproteins in behavior. These diminutive lipids like particles are frequently taken through endogenous lipid absorption mechanism through enterocytes of GIT tract.[14] Intestinal absorption of long-chain triglyceride from enterocytes is a complex incident that includes the co-ordination of synthesis of apolipoproteins and lipids and their intracellular assembly into mature lipid-containing particles.[15] The major digestive products of triglyceride are monoglycerides and free fatty acids. These are absorbed into the enterocytes via passive diffusion and transported within the enterocyte to the endoplasmic reticulum (ER), where biosynthesis of complex lipids to form triglyceride takes place. [16] The precursors of chylomicrons, termed prechylomicrons, are synthesized in the ER and Golgi apparatus. Lipoproteins are made in the ER and then transported to the Golgi. The chylomicrons then migrate to the lateral membrane of enterocytes and are exocytosed, and the triglyceride-rich lipoproteins are discharged into the intercellular space.[17] Lipid-based excipients can influence oral absorption via various physiological effects such as retarded gastric emptying,[18] stimulating bile flow, and secretion of pancreatic juice increasing the membrane lipid fluidity or acting directly onto enterocytes-based drug transport and disposition.[19-21]

Emulsomal formulation

Lipid core

An essential component of emulsomes is an internal hydrophobic core or lipid core comprises lipid, which exhibits solid or lipid crystal phase or mixed solid and liquid crystal phase at room temperature (25°C). There are abundant lipids or lipid like excipients available commercially. All of which are collectively called lipids in the pharmaceutical field.[22] The lipid used may be single or mixture of lipids. They are fatty acids and their derivatives or substances biosynthetically and functionally related to these compounds.[23-25] Lipids are generally insoluble in water and are often identified by their fatty acid composition, melting point, and hydrophilic-lipophilic balance (HLB). Lipids with low HLB and high melting point are suitable for sustained release. Whereas, the semi-solid excipients and those with high HLB serve as immediate release and bioavailability enhancement excipients.[26-29] Triglycerides which are solid at 25°C are found to be appropriate core material because these lessen the acceptable storage life of o/w emulsion. The triglycerides are used for preparation of emulsome composed of un-branched fatty acid with chain length in the c-10 to c-18 range.[30]

Antioxidant

The lipid core of emulsome particles of this invention optionally may contain one or more antioxidant. The preferred antioxidant is a-tocopherol or its derivative, which are members of vitamin E family. Other antioxidants include butylated hydroxytouline (BHT). Antioxidants lessen the formation of oxidative degradation products of unsaturated lipids such as peroxides. The need of antioxidant may be protected by preparing the lipid core form saturated fatty acid.[30]

Negatively charged particles

Negatively charged lipid particles such as oleic acid or negatively charged phospholipids such as phosphatidic acid, phosphatidylinositol, and phosphatidylsterine can be imparted to emulsomes to raise the zeta potential of the composition, thus stabilizing the particles. Additionally, the incorporation of these negatively charged lipids compounds in emulsomes result in the formation of phospholipids bilayers with opposing charge.[30] Thus, increasing the loading aqueous compartment formed by the phospholipids bilayers surround the lipid core. This effect results from the layers aqueous space between the bilayers cause electrostatic repulsion between them. Negative charge reduces the particles aggregation, which minimizes the coalescence, floccation, or fusion.[31]

Surfactants

Selection of surfactant should be done on the basis of Hydrophilic Lipophilic Balance (HLB) value. As HLB is a good indicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation.[32] Transition temperature of surfactants also affects the entrapment of drug in vesicles. Spans with highest phase transition temperature provide the highest entrapment for the drug and vice versa.[33,34] The drug leaching from the vesicles is reduced due to high phase transition temperature and low permeability.[35] High HLB value of Span 40 and 60 results in reduction in surface free energy, which allows forming vesicles of larger size and hence large area exposed to the dissolution medium.[36-38]

Phosphatidyl choline

Phosphatidyl choline is such a major component of lecithin. Phosphatidyl choline has low solubility in water. In aqueous solution its phospholipids can form bilayer sheets, micelles, or lamellar structures, depending on hydration and temperature. This results in a type of surfactant that is usually classified as amphipathic. They are a major component of biological membranes and can be easily obtained from a variety of readily available sources such as egg yolk or soya beans. Depending upon the source from which they are obtained they are named as egg lecithin and soya lecithin. Incorporation of lecithin further enhanced the percent drug entrapment to 96.1% and leads to vesicles of smaller size due to increase in hydrophobicity, which results in reduction of vesicle size.[39]

Cholesterol

Cholesterol is essential component of emulsomes as vesicles. Incorporation of cholesterol influences vesicles stability.[40,41] Concentration of cholesterol plays an important role in entrapment of drug in vesicles.[42,43] There are reports that entrapment efficiency increase with increasing cholesterol content. It was observed that with very high cholesterol content had a lowering effect on drug entrapment to the vesicles.[44] This could be due to the fact that cholesterol beyond a certain level starts disturbing the regular bilayer structure leading to loss of drug entrapment.[45] Various materials used for emulsomal preparation along with their uses are given in Table 1.

Methods of preparation

Lipid film formation (Hand shaking method)

In this method surfactants/lipids are casted as layers of film form their organic solution using flask rotary evaporator under reduce pressure (or by hand shaking) and then casted films are dispersed in aqueous medium.[46] Upon hydration, the lipids swell and peel off from the wall of round bottom flask at temperature slightly above the phase transition temperature of surfactants used for specific period of time (time of hydration) with constant mild shaking. The mechanical energy is required for the swelling of lipid and dispersion of casted lipid film is imparted by manual 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) while non shaking method produced large unilamellar vesicles (LUVs). Various methods for emulsomal formulations are shown in Figure 2.[47]

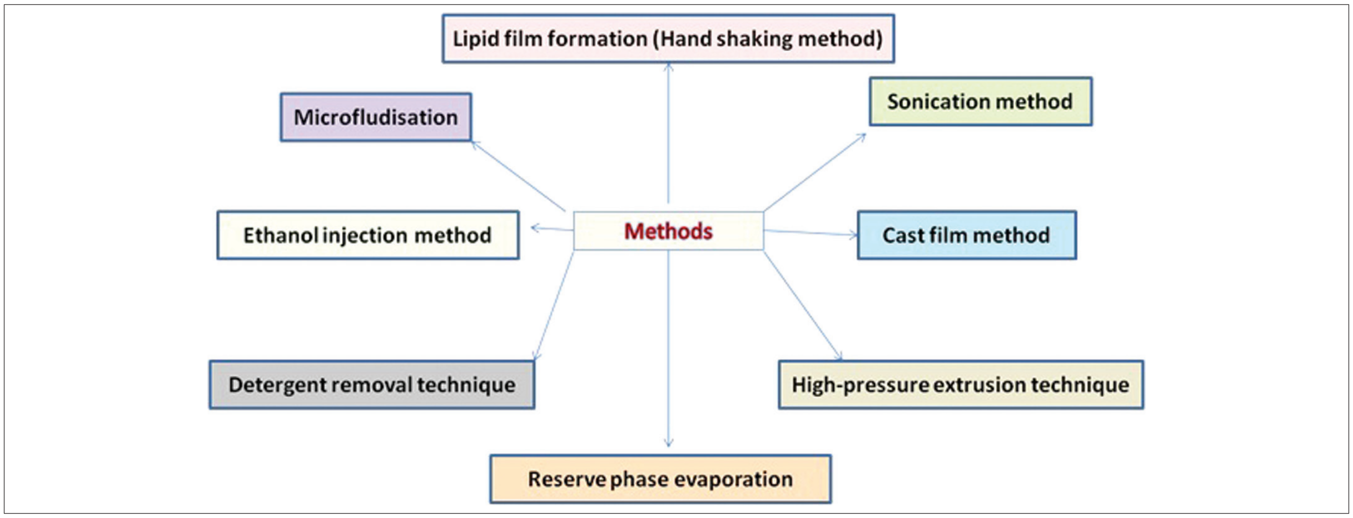

Figure 2: Methods of emulsomal formulation

Table 1: Materials for emulsomes formulation

Materials	Uses	References
Triglycrides	Used as hydrophobic lipid core, Lipids with low HLB value provides sustain released formulation.	[9,10]
Cholesterol	Incorporation of cholesterol influence vesicles stability, excessive cholesterol leads to un-stability of the formulation.	[32]
Soya lecithin	Bilayer sheets, micelles or lamellar structures and also increases the entrapment efficiency.	[31]
Stearyl amine	Impart positive charge for target delivery and raised the zeta potential of formulation.	[32]
Antioxidants	Protect the lipids from oxidation or rancidity.	[30]
Surfactants	Provide the highest entrapment for the drug.	[29]
Charged particles	Zeta potential of the composition, stabilizing the particles and reduce the particles aggregation.	[10,14]

Reserve phase evaporation

This technique, so-called 'reverse-phase evaporation' or REV method is comprised of two steps. Prepare a water-in-oil emulsion of phospholipids and buffer in excess organic phase. Remove organic phase under reduced pressure. The two phases (phospholipids and water) are usually emulsified by mechanical methods or by sonication. Removal of the organic solvent under vacuum causes the phospholipid coated water droplets to come together to form a gel-like matrix. Further removal of organic solvent, under reduced pressure, causes the gel-like matrix to form into a paste of smooth consistency. This paste is a suspension of LUV.[48] Drug entrapment efficiencies up to 60-65% can be achieved by this method. This method was used to encapsulate both small and large molecules.[49] The main disadvantage of this method is the exposure of drug to be encapsulated to organic solvents and to mechanical agitation. In this procedure, phospholipids are dissolved in organic solvents such as chloroform, isopropylether, or freon. In order to promote conditions for good emulsification, it may sometimes be required to 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.

High-pressure extrusion technique

It was demonstrated by several researchers that when MLV are repeatedly passed through very small pore polycarbonate membranes (0.8 to 1.0 pm) under high pressure the average diameter of the vesicles become progressively smaller reaching a minimum of 60-80 nm after 5-10 passes. As the average size is reduced the vesicles tend become unilamellar. [50-52] Similar results are noted by other investigators when MLV were passed through a Microfluidizer. Microfluidizer is an instrument that forces the feed material under high pressure through a narrow orifice. It appears that when MLV are forced through the small orifice, layers of bilayers are removed from the vesicular structure, as if the layers of onion skin are separated when it is peeled. It was also suggested that the mechanism of layer separation is only applicable to vesicles made with positively charged phospholipids and the vesicles that are greater than 70 pm in size.[53]

Sonication method

Solid lipids, cholesterol, and phosphatidylcholine in different molar ratios were taken in a round-bottom flask and dissolved in a minimum quantity of chloroform containing 3 or 4 drops of methanol. To this solution, an accurately weighed quantity of drug was dissolved. The organic solvent was evaporated until complete dryness under reduced pressure using a rotary evaporator to form a thin lipid film on walls of the round bottom flask.[54-56] The dried film was hydrated with phosphate-buffered saline pH 7.4 (10 mL) and homogenized by ultrasonication for 15 minutes at 40% frequency to obtain emulsomes of nano-size range.[9,10,14]

Cast film method

Emulsomes may be prepared by mixing phospholipids and triglycerides in a weight ratio range 0.5:1.0 where in the triglycerides has 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 otherwise reducing 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 preferably determined on a weight percentage basis rather preferably are determined on a weight percentage basis rather than a particle number basis. Conventionally the lipid component may be volatile and chemically un-reactive volatile organic solvent such as dichloromethane or diethylether. The solvent is removed typically under reduced pressure in a rotary evaporator or under stream of inert gas. The resulting lipid film is 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. The lipid suspension or dispersion is then sized typically by high shear homogenizer at a pressure up to 800 bars.[30]

Ethanol injection method

This method has been reported as one of the alternatives used for the preparation of small unilammellar vesicles (SUVs). In this method, an ethanol solution of surfactant is injected rapidly through a fine needle into excess of saline or other aqueous medium.[57] Vaporization of ethanol leads to the formation of vesicles. In the ethanol injection method a 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. The ethanol injection method is a suitable technique to obtain the spontaneous formation of emulsomes having a small average radius.[58,59]

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.[60,61] 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.[62-64]

Detergent removal technique

In this method, phospholipids and a detergent are mixed together to form micellar mixtures. Then the detergent removed from the preparation while the micelles progressively become richer in phospholipid content and finally the lipids come together to form single bilayer vesicles. Methods such as dialysis, column chromatography, or adsorption onto bio beads can be used to remove the detergent from the preparation. The dialysis technique was first reported for reconstituting biological membranes solubilized with detergents.[65] This method is applicable for the preparation of emulsomes also. Detergents that are commonly used for this purpose are those that have high critical micelle concentration (CMC). Materials such as sodium cholate, sodium deoxycholate, and octylglycoside and other detergents of high CMC (in the order of 10-20mM) are suitable detergents for this work.[66] In technique, detergent was removed by a flow through dialysis cell from phospholipid detergent mixture. It was reported that this technique yielded homogeneous population of single layered emulsomes with mean diameters of 50-100 nm.[67,68]

Biopharmaceutical aspects

Emulsomes helps increasing the in-effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts and endogenous biliary lipids including phospholipid and cholesterol, leading to the formation of bile salts/phospholipid/cholesterol intestinal mixed micelles and leads increase in the solubilisation capacity of the GI tract. However, exogenous lipids into these bile salts structures either directly or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilisation capacity.[69] Therefore, on the stimulation of intestinal lymphatic transportation, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism.

Emulsomes may enhance bioavailability by changing the biochemical barrier function of the GI tract. It is clear that the lipids and triglycrides, which are incorporated in emulsomal preparation may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump and may also reduce the extent of enterocyte-based metabolism.[70,71]

Emulsomes may change the physical barrier function of the GI tract. Various combinations of lipids and triglycerides have been shown to have permeability enhancing properties.[72,73] However, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble and lipophilic drugs.

Stability aspects of emulsomes

Emulsomes have the characteristics of both liposomes and emulsions; provide the advantages of high loading of hydrophobic bioactive compounds in the internal solid lipid core and the ability to encapsulate water-soluble drugs or antigens in the aqueous compartments of surrounding phospholipid layers.[14] The pharmaceutically stable emulsomes may be formulated in the absence of any ionic or non-ionic non-natural synthetic surfactants or cosurfactants such as polyoxamers, deoxycholate, polysorbates, etc. They are stabilized by the combination of relatively high lecithin content and the use of solid lipid compositions as the core.[13] The particle size distribution of emulsomes is based on differential weight percents in the range of 10-250 nm, making them suitable for parenteral administration by adding in water for injection.

Whereas oral vesicular formulations are generally instable, mainly due to leakage and potential destruction in gastric fluids. Emulsomes are a dry free-flowing powder when it comes in contact with water. The stability problems associated with conventional liposomes or other vesicular delivery systems are aggregation, susceptibility to hydrolysis, and oxidation. These problems may be avoided by using emulsomes.[10,13] Since emulsomes exist as a dry powder and upon hydration they are more suitable for developing sustained release formulations for oral delivery.

Important factor related to stability is zeta potential; the measurement of zeta-potential in electrostatically stabilized vesicles is the key factor to understand the application of the dispersion and aggregation processes and certainly is an important criterion for study of the storage stability of these vesicles.[9,10] Change in the lipid type, increased the absolute value of zeta-potential whereas in emulsomes, fats used trilaurin, tristearin, and comptriol ATO 888 provide a great negative value of zeta potential.[9,10,14] Therefore, decrease in particle size and zeta potential due to high input energy during sonication provides stable and highly packed emulsomes.

Application of emulsomes

Drug targeting

One of the most useful aspects of emulsomes is their ability to target drugs. Emulsomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelial system preferentially takes up Emulsomes. The uptake of Emulsomal vesicles is controlled by circulating serum factors called opsonins. These opsonins mark the vesicles for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver.[74] Emulsomes can also be utilized for targeting drugs to organs other than the reticulo-endothelial system. A carrier system (such as antibodies) can be attached to vesicles to target them to specific organs.[75]

Anti-neoplastic treatment

Most antineoplastic drugs cause severe side effects. Emulsomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Emulsomal entrapment of Methotrexate showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination. Table 2 shows various studies done on emulsomes as delivery system.[76,77]

Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonials), which in higher concentrations can cause cardiac, liver, and kidney damage. Use of emulsome in tests conducted showed that it was possible to administer higher levels of the drug without triggering the side effects, and thus allowed greater efficacy in treatment.[78,79]

Used in biotechnology

Emulsomes are used in studying immune response due to their immunological selectivity, low toxicity, and greater stability. They are being used to study the nature of the immune response provoked by antigens. The *in vitro* permeation of estradiol from vesicular formulations through human

Table 2: Different studies related to emulsomes as carrier system

Pharmacological class	Description	References
Anticancer (Methotrexate)	Emulsomes showed promising potential for delivery of methotrexate. Formulations should also be protected from harnessing gastric environment of stomach before oral administration. A much higher bioavailability of methotrexate may be achieved successfully with lipid based emulsomes.	[10]
Anti-fungal (Amphotericin B)	Amphotericin B emulsomes displays better antileishmanial activity. The study also demonstrates that the efficacy of Amphotericin B against visceral leishmaniasis is increased if the drug is used in the OPM-grafted emulsome form.	[14]
Anti-fungal (Amphotericin B)	Emulsomes-based systems showed excellent potential for intracellular macrophage targeting. The formulations could significantly modify the pharmacokinetics of AmB, providing prolonged action at comparatively low drug doses thereby reducing the toxicity problems like nephrotoxicity, cardiac arrhythmia etc.	[13]
Anti-viral (zidovudine)	Catoionic Emulsomes were developed which showed excellent potential for Intracellular hepatic targeting. The formulations could significantly modify the pharmacokinetics of zidovudine, providing prolonged action at comparatively low drug doses.	[9]

stratum corneum was studied. The vesicles were composed of non-ionic n-alkyl polyoxyethylene ether surfactants. Two mechanisms are proposed to play an important role in vesicle-skin interactions, i.e., the penetration enhancing effect of surfactant molecules and the effect of the vesicular structures caused by their adsorption at the stratum corneum- suspension interface.[80]

Future aspects

Emulsomes are a promising approach for the formulation of drug compounds with poor aqueous solubility with varied oral bioavailability. The oral delivery of hydrophobic drugs can be made possible by emulsomes, which have been shown to substantially improve oral bioavailability. Renaissances in the use of emulsomes over the past few decades are inviting increasing attention. Recent trends are focused on the development of modified emulsomal solid or semisolid formulations as an alternative to the conventional liquid system. The development of emulsomes, however, is still largely empirical, and *in vitro* models that are predictive of oral bioavailability enhancement are lacking. There is a need for *in vitro* methods for predicting the dynamic changes involving the drug in the gut in order to monitor the solubilisation state of the drug *in vivo*. Attention also needs to be paid to the interactions between lipid systems and the pharmacologically active substance. The characteristics of various lipid formulations also need to be understood, so that guidelines can be established that allow identification of suitable candidate formulations at an early stage. Future research should involve human bioavailability studies as well as more basic studies on the mechanisms of action of this fascinating and diverse group of formulations.

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