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Review Article

Liposome as a Targeted Drug Delivery System

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ABSTRACT

Recent developments in 'drug delivery systems are primarily focused on smart drug delivery, which focuses on drug administration at the appropriate time, dosage and location with maximum safety and efficacy. Targeted drug delivery system is advanced method of delivering of drugs to a specific site like infected organ, tissue or cell. In this system the medication is transported or concentrated selectively at the site of action to localize the interaction of drug with diseased site and to avoid the harmful effects to healthy tissue due to drug interactions. Seeks to concentrate the medication in the tissues of interest while reducing the medication in the remaining tissues, drug is delivered to a specific location rather than the whole body and organ. The end goal is improving treatment effectiveness while reducing side effects. The targeted studied drug delivery system also called as Smart drug delivery system. The Liposome is used as drug carrier for targeted drug delivery system. liposomes are the mostly because of their biocompatibility, biodegradability and low toxicity. Liposomes as a carrier for drug delivery approaches have various advantages like, they are able to mask compound, liposomes protect drugs from degradation. Liposomes are suitable for the controlled release; liposomes also increase the efficacy and therapeutic index. liposomes can be easily penetrate and effectively deliver to targeted area.

INTRODUCTION

Targeted drug delivery system is a smart delivery system has various advantages as compared to conventional drug delivery system like, Toxicity is reduced by delivering drug to its target site, thereby reducing harmful systemic effects. Drug can be administered in a smaller dose to produce the desire effects; there is avoidance of first pass metabolism and enhancement of the absorption of target molecules such as peptides and particulates. Dose, is less as compared to conventional drug delivery system. There is no peak and valley plasma concentration, selective targeting to infections cells that compare to normal cells. Liposomes is used as targeted drug delivery.

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Approaches of drug delivery

1) Passive targeting

Passive Targeting Targets The. Systemic Circulation. In this technique, drug targeting occurs because of the body's natural response to 10 drug-carrier system. Physicochemical characteristics of the drug Based on the accumulation of drug at areas targeting the site of interest, such as in the case of tumour tissue. Accumulation of drugs or drug carrier systems at the intended site of action by the action of physicochemical and physiological factors is passive targeting. Passive targeting is present naturally in the human body. Nanoparticles are used as carriers in passive targeting and they are directed to enter blood vessels more at the disease site, which provides the opportunity for significant drug accumulation at the target[2].

2) Active targeting

In this active targeting approach carrier system bearing drug reaches to specific site on the basis of modification made on its surface rather than natural uptake by Reticuloendothelial System (RES). Surface modification technique include coating of surface with either a bjoadhesive, non-ionic surfactant or specific cell or tissue antibodies (i.e, monoclonal antibodies). Or by albumin protein". Active targeting can be classified into different orders of targeting

a) First order targeting- In first order targeting there is limited distribution of the drug-carrier system to the capillary bed of the target site[3]. Example-organ or tissue.

b) Second order targeting- second order targeting refers to the selective provision of drugs to specific cell types, such as tumor cell.

C) Third order targeting- third order targeting intracellular sites specifically intracellular organelles.

d) Fourth order targeting- fourth order targeting is sometimes nominated for drugs targeting macromolecules, such as DNA and proteins.

3) Inverse targeting

In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by RES and hence the process is referred as inverse targeting. To achieve inverse targeting RES normal function is suppressed by pre injecting large amount of blank colloidal carriers or macromolecules like dextran sulphate. This approach leads to saturation of RES and suppression of defence mechanism. This type of targeting is an effective approach to target drug to non-RES organ[3].

4) Ligand mediated targeting

In this ligand mediated approach ligands are used as carrier surface group, which can selectively direct the carrier to the pre-specified site housing the appropriate receptor units to serve as homing device to the carrier or drug. Most of the carrier systems are colloidal in nature and can be specifically functionalized using various biologically relevant molecular ligands including antibodies, polypeptides, oligosaccharides, viral proteins and fusogenic residues. Ligands confer recognition and specificity upon drug carrier and provides them with an ability to approach the respective target selectivity and deliver the drug. Example. Folate receptor-overexpression of folate receptor.

5) Physical targeting

Physical targeting is a delivery system that releases the drug only when exposed to a specific microenvironment such as change in PH or

environment or the use of external magnetic field. This Approach was found exceptional for tumour targeting as well as cytosolic delivery of entrapped drug or genetic material.

6) Chemical Targeting

Chemical targeting involves the localization of agents to targeted areas through the use of site-specific prodrugs. Agents can also be directed to areas through the use of enzymatic or chemical reactions that lead to the targeting of a vehicle or the controlled release or action of the agent.

7) Biological targeting

Biological targeting allows localized agents to target areas through the use of antibodies, peptides, proteins, or other biomolecules that have affinity with receptors, sites, or other biological targets in a specific manner.

8) Dual Targeting

In dual targeting approach carrier molecule itself have their own therapeutic activity and thus increase of drug the therapeutic effect for example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

9) Double Targeting

To a carrier system. In double targeting temporal and spatial methodologies are combined, i.e., spatial placement to specific sites and temporal delivery at a controlled rate. Temporal and spatial methodologies are combined target Spatial placement relates to targeting drugs to specific organs tissues, cells or even subs cellular compartment. Temporal delivery refers to controlling the rate of drug delivery to target site,

10) Combination Targeting

The combination targeting is equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to target site.

11) Local Targeting

locally targeted systems are noninvasive targeting strategies with the principal goal of delivering the drug to the local site for the management of local pathologies.

12) Systemic Targeting

Delivery of such therapeutic systems occurs through an invasive route, such as intravenous administration of nanotechnological systems.

Major limitations- adverse effects of the drugs in a specific tissue.

13) Location based and Disease based Targeting

It is a targeted delivery to specific cells, organs and organelles. Intracellular targeting, gastrointestinal tract (GIT) targeting, brain targeting the respiratory tract. Disease based targeted delivery is a site-specific therapy targeting tumors and other targetable infectious diseases. Tackling infections using nano-DDSs could provide a practical alternative to antibiotic therapy.

Benefits of targeted drug delivery

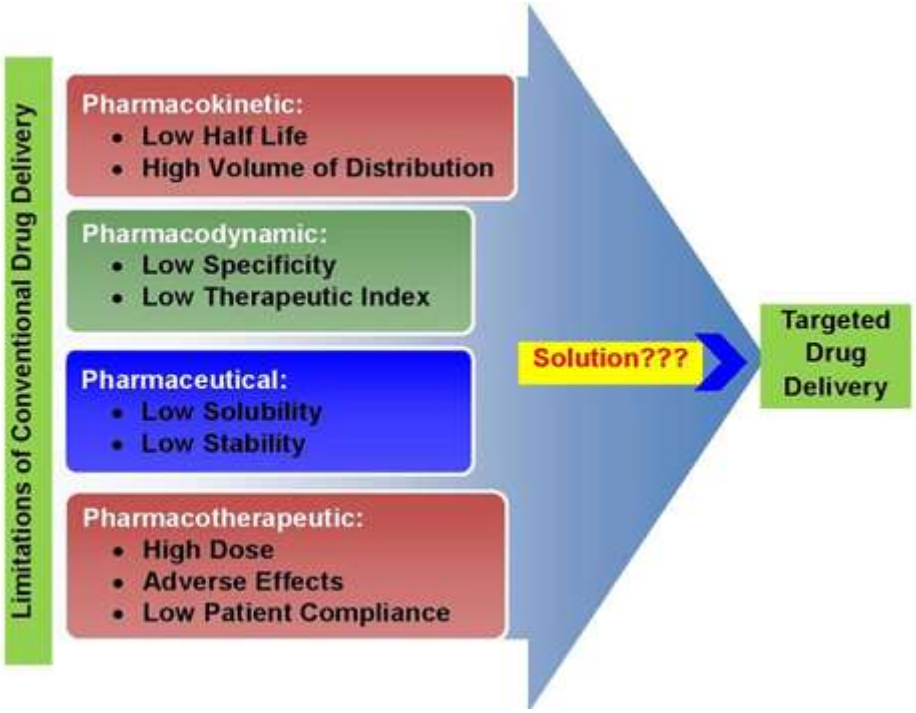

Figure 1: Benefits of targeted drug delivery

LIPOSOME

Liposomes used as targeted drug delivery system because it has various merits. Liposome consist of two Greek word Lipos means fat and Soma means body. Liposome consist of phospholipid which is component of cell membrane, Due to amphiphilic nature of phospholipid liposome become good candidate for drug delivery[2]. Liposomes were first produced in England in 1961 by Alec D. Bangham. Liposomes are simple microscopic vesicles in which the therapeutically Active ingredient are enclosed by a membrane composed of lipid molecule. structurally, liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayers mainly composed of natural or synthetic phospholipids. Phospholipid are the major component of biological. Cell Membranes.

Self-assembled Phospholipid Bilayer Structure of Liposome

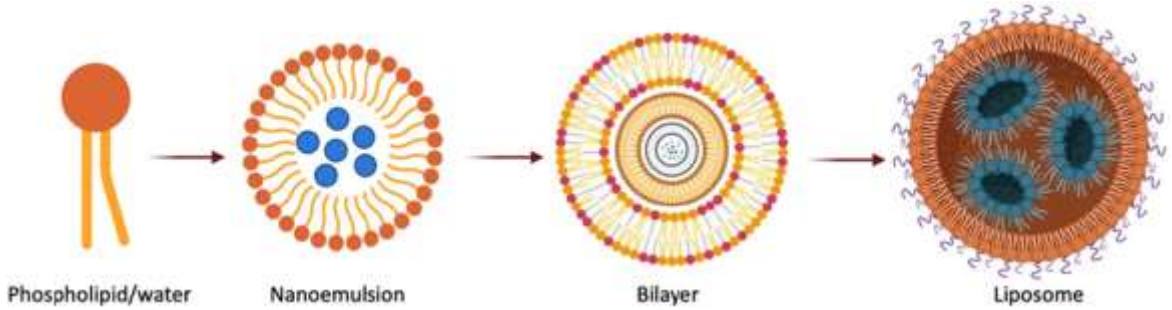

Figure 2: Structure of liposome

The rationale of encapsulating a drug within liposomes is to prevent its rapid metabolism and its rapid removal from blood circulation after its administration so that the drugs from depot liposomes are ideally suited for drug delivery. Liposomes provide selective passive targeting to tumor tissues (liposomal doxorubicin), increased stability via encapsulation. Reduction in toxicity

of the encapsulated agent. Flexibility to couple with site specific ligand to achieve active targeting[3].

Composition of liposome

Liposomes has been composed of two components i.e, phospholipids and cholesterol

1) phospholipids

Phospholipid is major component of the biological membrane; two types of phospholipids are used natural and synthetic phospholipids. The most common natural phospholipid is the phosphatidylcholine (PC). phospholipids are amphipathic (having affinity for both hydrophilic and hydrophobic part) molecule and also known as Lecithin. Phospholipid molecules has hydrophobic tail and hydrophilic polar head.

2) Cholesterol

Cholesterol is useful in stabilizing the membrane, incorporation of cholesterol in liposome bilayer can bring about big changes in the preparation of membrane.

Cholesterol enhances the rigidity of the phospholipid bilayer, it can reduce the permeability of water-soluble substance".

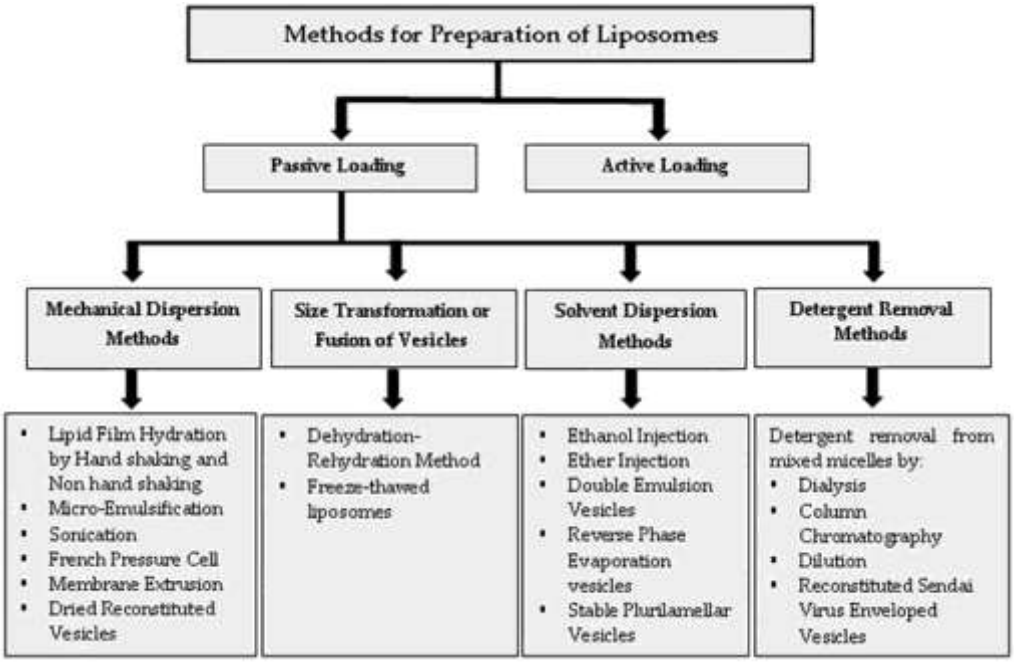

Figure3: Methods of liposome preparation

1) Mechanical dispersion method

a) Lipid film hydration

For preparation of liposomethe lipid should be dissolve and mix in organic solvent for homogeneous mixture of lipids. usually, this method is carried out by using chloroform or chloroform methanol mixture. The lipids are mixed in the organic solvent, the organic solvent is removed by means of evaporation using nitrogen or argon stream in a fume hood, for larger amounts the organic solvent should be removed by using arotary evaporator at reduced pressure. Finally, the lipid film deposited on the sides of round bottom flask. The lipid film is dried to remove organic solvent by placing the flask on a vacuum pump for overnight.it is hydrated by adding an aqueous buffer solution under agitation which gives multilamellr liposomes.

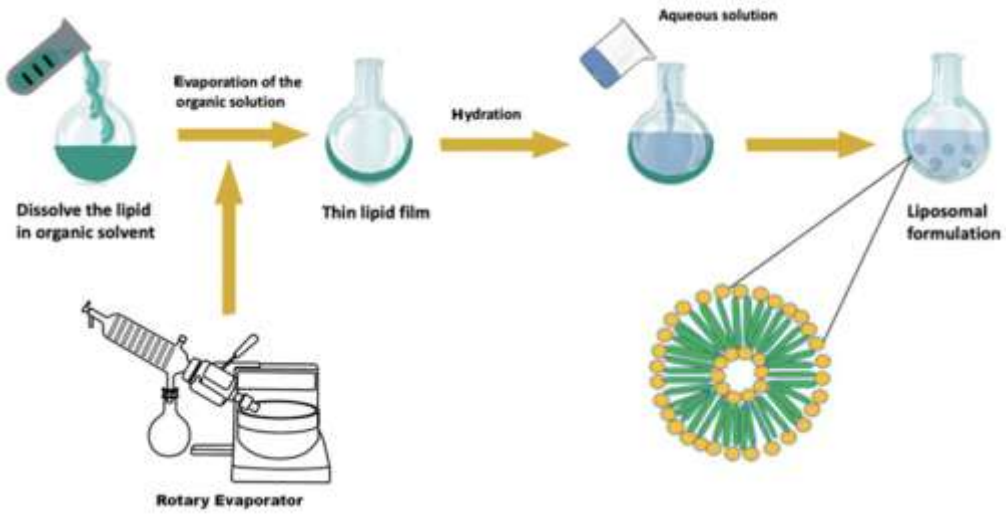

Figure 4: Lipid film hydration method

b) Micro emulsification method

A lipid dispersion is placed in a microfluidizer pump which pumps the fluid at 600-700 bar pressure through a 5-micrometer orifice Then this dispersion is forced along micro channels, which make two streams of fluid collide with each other at right angles at a high velocityand Due to this transfer of energy takes place resulting in formation of multilamellar vesicles.

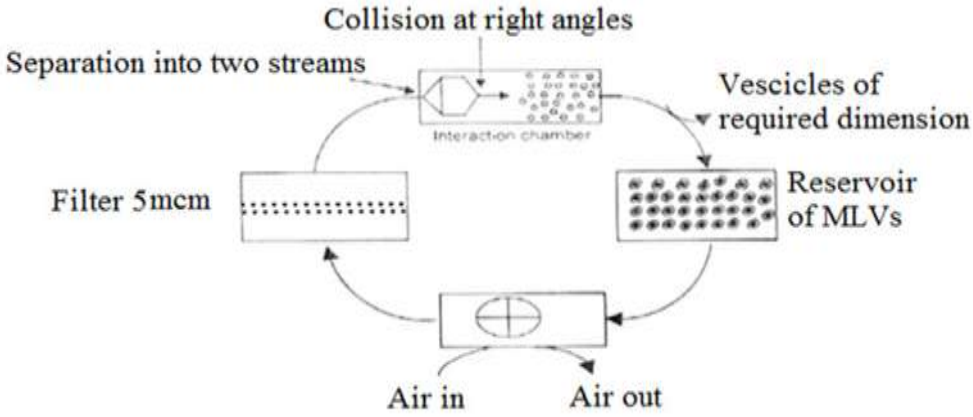

Figure 5: micro emulsification method

Sonication:

In this method MLVs (multilamellar large vesicles)are exposed to UV radiations to get small vesicles. There are two methods of sonication i.e, bath sonication and probe sonication.probe is used for high concentrated lipids while bath is used for large volumes of diluted lipids. In probe a high energy is used which may result lipid degradation. For these reason bath sonicator are used for preparation of MLVs. In this method dispersion is placed in a test tube which is placed in a sonicator. Sonication is done for 5-10 min until a transparent solution appears. After sonication dispersion is placed in a plastic centrifugation tube and cetrifused for 30 min at 20-degree celcius to get large MLVs and 3-4hours to get SUVs (small unilamellar vesicles). In this method an ethanol solution of lipids is injected rapidly into an excess of saline or otheraqueous medium through a fine needle. The force of injection is sufficient to achieve complete mixing so that ethanol is diluted

instantaneously in water and phospholipid molecules are dispersed evenly in medium.this procedure yields high proportion of SUVs (25nm). In this method there is low risk of degradation of sensitive lipid.

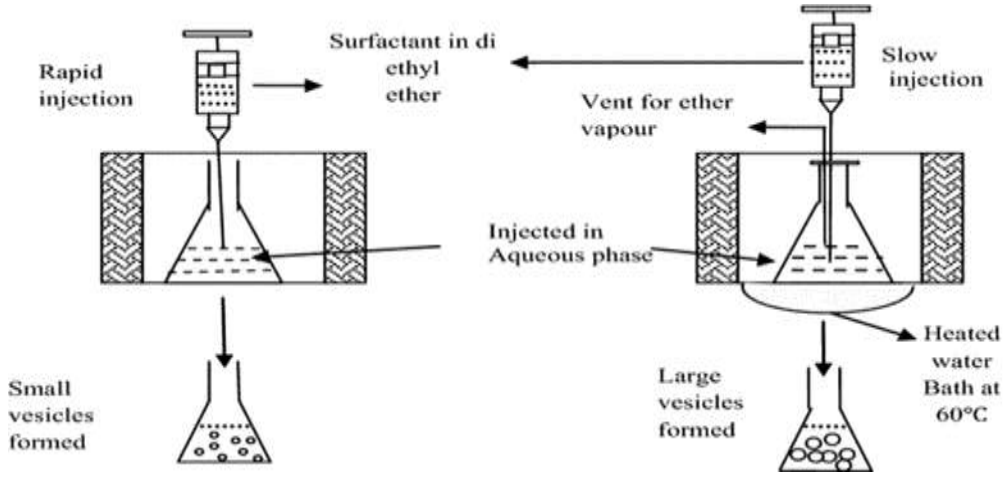

Figure 6: formation of liposome by Sonication

2) Solvent Dispersion method

a) Ether injection

This method involves the immiscible organic solution very slowly into an aqueous phase through a narrow needle at the temperature of vaporizing the organic solvent 10

3) Detergent removal methods

In contrast to phospholipids detergents are highly soluble in both aqueous an organic media. Equilibrium is indicated by critical micelle concentration. Lowering the concentration of detergent in the bulk aqueous phase, the molecules of detergent can be removed from mixed micelle by dialysis. High CMC (critical micelle concentration) indicate equilibrium shifted to bulk solution removal by dialysis easy. Commonly used detergents are sodium cholate and sodium deoxycholate10.

APPLICATIONS OF LIPOSOME

Various liposomal drug delivery systems have been developed with different mode of drug delivery for pathogens such as tuberculosis, salmonellosis, herpes simplexvirus, leishmaniasis, histoplasmosis and cryptococcosesto.

➤ In gene delivery

➤ In cosmetics and dermatology

➤ Industrial application of Liposomes

➤ In diagnosis

➤ In cell delivery

➤In immunology

➤ In lymphatic targeting

➤ Used in artificial blood surrogates

➤ Liposomes used in eye disorders

➤ Liposomes used as vaccine adjuvants

➤ Liposomes used in tumor therapy

➤ As antibiotic

➤ Used in respiratory drug delivery system”

Therapeutic application of liposome

Drug	Route of Administration	Application	Targeted Disease
Amphotericin B	Oral delivery	Ergosterol membrane	Mycotic infection
Insulin	Oral, ocular, pulmonary and transdermal	Decrease glucose level	Diabetic mellitus
Ketoprofen	Ocular delivery	Cyclooxygenase enzyme inhibitor	Pain muscle condition
Pentoxyfyllin	Pulmonary delivery	Phosphodiesterase	Asthama
Tobramycin	Pulmonary delivery	Protein synthesis inhibitor	Pseudomonas infection, aeruginosa
Salbutamol	Pulmonary delivery	B2 adrenoreceptor antagonist	Asthama
Cytarabin	Pulmonary delivery	DNA polymerase inhibition	Acute Icukaemia
Benzocaine	Transdermal	Inhibition of nerve impulse from sensory nerves	Ulcer on mucous surface with pain
Ketoconazole	Transdermal	Inhibit ergosterol membrane	Skin disorder Candida albicans
Levanogesterol	Transdermal	Rhamnose receptor	Urtecaria, allergic skin disorder
Hydroxyzine	Transdermal	H1-receptor antagonist	Ibuprofen
Ibuprofen	Oral delivery	Chaemoreceptor, free ending	Rheumatoid arthritis

Marketed Products of Liposome

Name	Trade name	Company	Indication
Liposomal amphotericin B	Abeket		Fungal infections.
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infection
Liposomal cytarabine	Depocyt	Pacira (formerly skyepharma)	Malignant lymphomatous meningitis
Liposomal dauno Rubicin	DaunoXome	DaunoXome	HIV-related kaposi's sarcoma
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal IRIV vaccine	Liposomal IRIV vaccine	Berna Biotech	Hepatitis A
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal morphine	DepoDur	Skyepharma, Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Dox1/Carlyx	Ortho Biotech, Schering plough	HIV-related kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy

CONCLUSION

This article reviewed the delivery of drug molecule to reach its specific site is itself a difficult task in complex cellular network of organism. Targeted drug delivery is coming forward as one of the brightest advanced technique the medical sciences in the diagnosis and treatment of various diseases. This article also reviewed that the methods of preparations of liposomes, and various

applications of liposomes in various diseases. Liposomes have gained extensive attention as Targeted drug delivery system. The development of liposomes as carriers for therapeutic molecules is an ever-growing research area. Liposomes have been realized as extremely useful carrier systems and tools in various scientific domains such as biophysics, biochemistry, chemistry, physics, physical chemistry, colloidal science, mathematics, biology, ecology, pharmacology and pharmaceutical sciences. The uses of liposomes in the delivery of drugs, genes and cell to the target sites are promising and may serve as a handle for focus of future research.

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