International Journal of
Pharmacy Practice & Drug Research
www.ijppdr.com

LIPOSOME: A NOVEL ADVANCEMENT IN DRUG DELIVERY

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ABSTRACT

Liposomes is considered the leading technique to be focused on to solve the problems that most of the drugs face today like dose control, sustain release, drug toxicity, gastric intolerance of drugs, in-stabilities of drug. Besides having some disadvantages, liposomes can serve as an advantageous method of drug delivery if efforts would be made in developing it accordingly. In the present article, all the research efforts in preparing and stabilizing the liposomes have been reviewed. A Brief note on the advancements, clinical, therapeutical and miscellaneous applications along with examples have been given. The current clinical trial information on the liposomes, their marketed formulations have also been added and can be studied in detail following the references cited in the article.

Keywords: Liposomes, Applications of Liposomes, Liposomal Formulations, Liposomal Stability, Novel Liposomal Techniques.

INTRODUCTION

Most of the present population all over the world suffers from many diseases and disorders which include from dreadful Cancer, Diabetes, Hepatitis, AIDS to very common Hormonal imbalances, topoical and systemic infections. There are many drugs available for the treatment of these diseases using appropriate delivery depending on the nature of the drug, duration of treatment, disease status etc.

The current conventional drug delivery systems were effective in treating all the diseases but with some remarkable drawbacks. The need for higher doses of drug for effective treatment, dose control, sustain release, drug toxicity, gastric intolerance of drugs, in-stabilities of drug etc., stands as hurdles for the drug delivery in achieving the required effect of the drug. So there is an urgent need to investigate newer and advanced methodologies to effectively deliver the drugs to overcome the mentioned drawbacks. This necessity has forced researchers to develop novel technologies like Serum proteins, Immunoglobulins, Synthetic polymers, Liposomes, Niosomes, Microspheres, Erythrocytes, Reverse micelles, Pharmacosomes, Monoclonal antibodies, *etc.* Among them, liposomes have a leading role in the effective delivery of drugs to target their action and in controlling the release at a predetermined rate. Formulation of drugs in liposomes has given an opportunity to enhance the therapeutic indices of various drugs mainly through the alteration of bio-distribution and drug targerting [1].

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LIPOSOMES

Liposomes are drug carrying vesicles containing concentric phospholipid bilayers circulating around aqueous compartment ranging from 50-1000 nm in diameter. Various drugs from low molecular weight (glucose, synthetic drugs, etc.) to high molecular weight (peptides and proteins, DNA, etc.) have been incorporated in liposomes. The water soluble/hydrophilic drugs are present in aqueous compartments while lipid soluble and amphiphilic drugs trap themselves in phospholipid bilayers. The liposomes containing drugs can be administrated by many routes (intravenous, oral inhalation, local application, ocular), can be delivered in many vehicles (creams, ointments, capsules, solutions, sprays, etc.) and these can be used for the treatment of many diseases (skin disorders, Diabetes, Cancer, infections, etc.) [2].

Preparation and stability

Liposomes are prepared by many methods and they have their own advantages and disadvantages. The liposomal preparation methods, types, advantages and disadvantages of the methods in terms of size distribution and encapsulation efficiency in detail have been reviewed by Mohammad Riaz [3]. One can get a note on the mechanism of liposomal fusion. The industrial scale preparation methods and the advantages have also been discussed. Number of researches provides the scientific evidance for a varied variety of lipids, their application in the preparation of liposomes. They finally push the stability of the prepared formulation as a big criterion to be improved as liposomes lack stability due to the phospholipids used in the preparation are instable. The factors affecting the stability and the influence of the concentration of lipids on the stability have been reviewed[4]. Physical and chemical stabilities of liposomes and the methods to improve the stability have been given. The potential uses of the liposomes have also been reviewed by Mohammad Riaz. The cholesterol concentration[5] and temperature effect on the stability and other variable parameters[6] influencing the stability of the formulation has been studied. It was proven that the Liposomes prepared of natural lipids are biodegradable, biologically inert, weakly immunogenic, produce no antigenic or pyrogenic reactions and possess limited intrinsic toxicity. Therefore, drugs incorporated in such liposomes are expected to overcome the rapid degradation and minimising side effects [4].

Advancements in Liposomes

There are various types of liposomes classified on the basis of the targeted site, technology used, and use. The drug release from the liposomal action occurs by different mechanisms and the targeting of the liposomes to a specific site is achieved in various ways. All the types, mechanisms of action and targeting strategies of the liposomes have been reviewed [5].

To overcome the drawbacks of the liposomes and to further enhance the drug delivery some advancement were made to conventional liposomes. This brought up the development of newer concepts like *Plarosomes*, featuring the approaches to target the Anthracycline drugs at the site of action, *Pulsatory liposomes* for the well-controlled delivery of biotechnological products, *Thermosensitive liposomes* in combination with localized hyperthermia, to improve the targeted drug delivery for more effective management of melanoma, *Gaint liposomes* for stability and the simulation of the cells models, *Dry liposomes* using sugars which stabilize the membranes by lowering lipid phase tranition temperature and prevent liposome aggretation and fusion, thus achieving a stable liposomal formulation. This stabilization mechanism was explained that the sugar molecules form hydrogen bonds with the polar heads of the phospholipids on the liposomal membranes, *Sterically stabilized liposomes*, challenging the stability problem. Detailed information on the preparation and evaluation of every type of liposomes stated above can be studied from the citations quoted against each type [6-9].

APPLICATIONS

The concept of liposomes being the most recent technology available for achieving controlled release, sustained action and targeted delivery is promising in satisfying the requirements of the most of the drug facing problems when it comes to the point of drug delivery. In consideration of the advantages liposomes are applied in the various fields of science.

Bio-technology

Liposomes offer a great use in all the fields of science and medicine. Especially in Bio technology considering the targeted action, they are claimed to be used extensively and effectively for the delivery of genetic material, antigens, viral coats and vaccines. It is a tedious work to develop a methodology to satisfy the issues that the delivery of biotechnological material demands but was found to be a complaint technique to meet the aspects. Various approaches for the effective delivery of nucleic acids and genetic material have been discussed [10-13]. The composition, and the influence of lipids on the liposomes, the methods of preparation and encapsulating the DNA into liposomes, their evaluation procedures have been revealed. Methods to access the pharmacological action, pharmacokinetic parameters and bio distribution have been reviewed.

Medical science

Liposomes have their application in the many fields of medicine like diagnosis and therapy. The major clinical applications include the treatment of cancer, antimicrobial therapy and gene therapy. The preceeding were explained in detail[1]. Besides a detailed note on the liposomal applications and the kinetics in the drug release have been reviewed. The mechanics in the action and efficacy of various drugs have been proved [14,15].

Cosmetics

Liposomes have their application in cosmetic industry wider than any other field. There are a lot of marketed preparations manufactured by different manufacturers that intended for the topical cosmetic use. Liposomes entrap a variety of active molecules like anti-oxidants, vitamins, natural or synthetic drugs, and can therefore be utilized for skin creams, anti-aging creams, after shave lotions, lipsticks, sun-screen and make-up creams [15].

Microbiology

Liposomal application in fermentation technology has yielded better results in the production of cheese, enzymes, antibiotics, etc. The total fermentation time can be considerably lowered and simultaneous production of the fermented products can be improved. This was explained with a classic example of cheese making. Enzyme protection can be achieved by encapsulating them into liposomes as it prevents the direct contact of the enzyme to the oxidants or compounds which cause degradation [16, 23-28].

Food industry

In food industry, natural antioxidants like vitamin C and E when used as a liposome formulation improves the activity of the compounds and reduce the use of artificial preservatives which cause unwanted side effecs [17].

Agro bio-ecological systems

Even agro-food industry employs liposomes in application to herbicides and pesticides by adopting the sustained release from the liposomes. This enables the prolonged contact time of the toxins to the pests thus ensuring the improved efficacy of the Herbisides and pesticides [18, 29-33]. Liposomes have found to be applicable in maintaining the ecological health to clear the oil leaks in the sea by liposomal trapped floating blooms [19-25]. The surfactant actions property of the liposomes coagulates the oil and sinks it into water and the degradation of carbohydrates in the oil by the bacteria encapsulated into liposomes was found more effective rather than the free cells. Interested readers can study liposomes in detail from the literature stated above and get more information on the applications through reference 20. Viewing these applications several drugs have been incorporated into liposomes and were reviewed in table.1

There are many approved liposomal drug formulations including the vaccines. They were tabulated in reference 12 page no. 10 and 13. The liposomal formulations under preclinical development and clinical trials were given in given in reference 12 page no. 12 and 13. Recent advances and the applications of the liposomes in cosmetics and drugs presently in Taiwan market have been reviewed [34-38]. Liposomal developments and the government rules and regulations to perform the trails on liposomes have been referred by Pei kan [39]. He also reviewed the current liposomal development that is taking place in industries, educational institutions and clinical trial status of this formulation [20-22].

Table 1: APPLICATIONS OF LIPOSOMES IN DRUG DELIVERY

Drug	Method of Preparation	Composition	Achievement	Reference
Ketaconazole	Thin film hydration	Soyalecithin, cholesterol tocopheryl acetate	Improve therapeutic response and reduce adverse effects	21
Acetazolamide	Reverse phase evaporation and thin film hydration	Egg phosphotidyl choline, cholesterol (steryl amine and diacetyl phosphate as + or – charge inducers)	Increasing the stability and reducing the intra ocular pressure	22

Drug	Method of Preparation	Composition	Achievement	Reference
N-Methyl-*N*-D-fructosyl amphotericin B methyl ester (MFAME)	chloroform film method	dimyristoyl phosphatidylcholine cholesterol or ergosterol	Reduction In toxicity of amphotericin B	23
Cyproterone acetate	solvent evaporation and thin film formation technique	phosphatidylcholine (PC): cholesterol	better penetration	24
Doxorubicin	Thin Film hydration method	Cholesterol Phosphatidylserhe, phosphatidylglycerol or cardiolipin Saturated or unsaturated Phospholipid acyl chains	Reduction I cardiotoxicity and enhanced antitumor activity	25
Ferrous sulphate	thin-film hydration, thin-film sonication, reverse-phase evaporation and freeze-thawing,	egg lecithin, 10% (mol/mol) cholesterol and 10% (mol/mol) Tween 80. Ascorbic acid	Increased electrostatic and steric stability	26
Hydroxyzine	Ethanol injection method and lipid film hydration method	L-α-phosphatidylcholine 95%(PC), cholesterol	Increase in drug concentration in skin and enhanced efficacy	27
Topotecan HCl	chloroform film method	soybean phosphatidylcholine or hydrogenated soybean phosphatidylcholine and cholesterol (PEG Ligated)	Improved stability and enhanced efficacy by accumulation in tumor cells	28
Paclitaxel	thin-film hydration method.	Soybean phosphatidylcholine (S100PC) and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine [methoxy (polyethyleneglycol)-2000]Cholesterol (CH)4 .C for further experiments.	Increased aqueous solubility	29
Pentoxifylline	chloroform film method	phosphatidylcholine (PC): cholesterol	Inproved bioavailability	30
Tranexamic acid (TA)	chloroform film method	hydrogenated soya phosphatidylcholine/ cholesterol/charged lipid {dicetyl phosphate (-) or stearylamine (+)}	Prolonged and sustained release	31

Drug	Method of Preparation	Composition	Achievement	Reference
5-fluorouracil	Solvent hydration method	(egg phosphatidylcholine (EPC) Cholesterol	Release stability	32
Natural and Biological products				
Drug	**Method of Preparation**	**Composition**	**Achievement**	**Reference**
Curcumin	chloroform film method	dimyristoyl phosphatidyl choline (DMPC) and cholesterol dipalmitoyl phosphatidylcholine (DPPC), egg phosphatidylcholine (EGG PC)	Enhanced anticancer efficacy	33
Recombinant human Interferon-α-2b	Reversed phase evaporation	Soya lecithin and cholesterol	Improved local retention and penetration	34
Components for protein synthesis	Freeze-thawing method	1-palmitoyl-2-oleoyl-*sn*glycero-3-phosphocholine,	Novelty in the protein expression	35
Insulin	freeze-thawing	Purified egg yolk phosphatidylcholine (PC), L-a-dimyristoyl phosphatidylglycerol (PG), and cholesterol (Chol)	Enhanced absorption from large intestine	36
Insulin (sodium insulin)	reverse-phase evaporation	dipalmitoyl phosphatidylcholine (DPPC), cholesterol	Enhanced pulmonary uptake and hypoglycemic effects	37
Artificial Viral Envelopes	Extrution method	1,2-dilauroyl-sn-glycero-3-phosphoethanolamine (DLPE), dioleoyl phosphatidyl serine (DOPS), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and Bovine sphingomylin (SM) from 100% fetal calf serum (FCS)	Reduction in lysis of AVE in serum	38

CONCLUSION

Controlled release and site specificity were considered important parameters for a drug to show its best efficacy. Developments have been made to achieve them and liposomes were considered leading technology in this field. Since the discovery of liposomes, the problems regarding the site specific targeting, drug entrapment, controlled release, storage stability and efficacy have been solved. They have played a significant role in improving the drug delivery and dose regulation of very potent drugs. Simultaneously many advances have been made to develop liposomes to patient's safety and compliance. It is expected that many conventional drugs will be benefited with their delivery in the liposomes. Gene therapy and vaccine delivery in liposomal delivery system would be promisingly advantageous and hopes for further developments.

ACKNOWLEDGEMNTS

Authors thank Dr. Arun Rasheed, Department of Pharmaceutical Chemistry, Sree Vidyanikethan college of Pharmacy, Tirupati for his motivation towards the work.

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