REVIEW ARTICLE

# Liposomal Drug Delivery Systems Have Opened a New Window in Pharmaceutical Sciences: A Literature-based Review

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**Abstract**

Widespread applications of liposome make it most interested carrier system of research and development than other available carrier systems. The lipids nanomedicine system was the first to make the concept of nanomedicine delivery into clinical approach that made them an established drug delivery system in present time for enormous success. In its application, liposome drug delivery usually targets directly to the tissue, which may contain target recognition molecules or not. This article is intended to give a brief overview of liposomal drug delivery system, its worldwide applications, and future perspective. Literature search results revealed applications of the liposome are in the immunology, vaccine and antigen, target delivery, delivery of insoluble or poorly drugs, delivery of nucleic acids, tumor therapy, and in combination therapy. At present, liposomal delivery is very popular in developed country, but we hope that, in future, the liposomal drug delivery system will revolutionize in all parts of the world to make the drug delivery system as perfect and effective as possible.

**Key words:** Clinical, drug delivery, immunology, insoluble, liposome, nucleic acids

## INTRODUCTION

Alec D. Bangham was the first man to get credit for the production of liposome. He produced liposome in England in 1961. Although we are using liposomal drug delivery system, it still makes it a topic of interest for further development of specific disease conditions. Liposomes are the small spherical shape vesicles produced from various lipids and sometimes with protein and act as a successful career for drugs to the specific target defined by Bangham *et al.*[1] Ability to deliver both hydrophilic and lipophilic substances is another criterion to be useful for delivery of non-toxic insoluble drugs.[2,3]

The idea of entrapping drug inside the vesicle of liposome and using it as a carrier for drug delivery was given and established by Gregoriadis.[4,5] Some of the earlier researchers also showed that how liposome could affect absorption and distribution of the entrapped drug in the body.[6-9] Various methods to produce large unilamellar vesicle (LUV) were also developed at that time and especially the important advancement of that time was to produce 100 nm pore size vesicles or <100 nm pore size with multilamellar polycarbonate filters.

The improvement of the liposomal drug delivery system by improving biodistribution of liposome throughout the body was made in the 1970s and 1980s. Such improvement was attained by increasing the stability of liposome, which leads it to give longtime circulation in the body after administering through intravenous route. In the 1970s, liposome was also used to consider that it can be used for the gene therapy in case of any genetic deficiency.[10] The components of liposome from which it is made up of are greatly matter for it's *in vivo* characteristics. According to the lamellarity, liposome is classified into two categories; "unilamellar" which contain only one phospholipid bilayer and "multilamellar" which contain multiple phospholipid bilayers in its composition. According to the size of vesicle liposomes, they are classified into small (≤100 nm), intermediate (100–250 nm), large (≥250 nm), and giant (>1 um). In case of characterizing liposome, there are

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mainly three parameters are needed to consider which are; physical, chemical, and biological parameters.

Not only in the field of drug delivery systems, but also liposome is achieving interest from researchers and pharmacist for its applications in cosmetics as well as in biological membrane.[11] A wide range of drugs can be entrapped inside the liposome to deliver the drug effectively in the target sites for potential therapeutic action as well as improved bioavailability (Figure 1). Various significant drugs such as drug for gene therapy, anticancer drugs, vaccines, antibiotics, genetic materials, proteins, and macromolecules can deliver through liposome due to its ability to encapsulate both hydrophobic and hydrophilic drugs.[12]

Since this is a literature-based review article, to complete this review, we have collected information from journals published in various reputed publishers such as PubMed, PubMed Central, Springer, Elsevier, Google Scholar, and other journal related to drug delivery system. We have used the keyword "liposomal drug delivery system" during search to get relevant information, and all information which is included in this article is cited with appropriate references.

## PROGRESSES IN PHARMACEUTICAL SCIENCES WITH THE INVENTION OF LIPOSOME

### Pharmacosome for the delivery of poorly soluble drugs

There is a complex named pharmacosome which is used to improve the bioavailability of less soluble or poorly soluble drugs. Pharmacosomes are made up of complex bond between drugs and amphiphilic phospholipids. In this bonding, there may be covalent, electrostatic, and hydrogen bonds are present.[14] Pharmacosome can be found in the form of micelle as well as hexagonal groups.[15] In case of dissolution drugs in the form of pharmacosomes are better than free drugs. A study showed that pharmacosome of aceclofenac give 10% better dissolution profile than free aceclofenac acid after analyzing through multiple methods.[14] Not only the dissolution rate, but also solubility was observed to be improved in pharmacosome than free acid form. According to the previous report, as the drugs stay inside the vesicle it improved the stability of the drugs. There is also the versatility of using pharmacosome-encapsulated drugs as it can administer orally, topically, and extra- or intra-vascularly.

### Receptor-mediated endocytosis through liposome

Receptor-mediated endocytosis was developed through the specific binding of antibodies to the target cells and in the liposome.[16,17] For specific binding of antibodies and liposome, there were several methods were being developed. A study conducted by Heath *et al*. showed that antibody-targeted liposome can significantly improve the toxicity of anticancer drugs to the culture cells.[18] Antibody-targeted liposome limited their distribution only to the target site and excreted from the body rapidly; thus, they show minimal toxicity. Another study also suggested that all components that reach to the target site cannot increase the concentration of drugs to the target.[19] Before liposome reaching to the target site, there are many obstacles such as types of tumor and number of physiological barriers need to be considered. Bonding to the tumor cells and tumor permeability are varied depending on the particle size of the liposome.[20,21] Attachment to the monoclonal antibody can regulate the distribution of the liposome in the brain. The coupling conjugate of liposome with brain drug transport vector passes the blood-brain barriers through receptor-mediated transcytosis and absorption regulated transcytosis. Another pharmaceutically desirable targeting is subcellular targeting to deliver efficiently after analyzing various pharmacokinetics and pharmacodynamics profiles of a drug.

### Liposome used in triggered release of drugs

There are various factors to explore triggers such as heat, ultrasound, light, enzyme, and pH; among them, triggers explored by heat, ultrasound, and light are called remote triggers; on the other hand, triggers explored by enzymes and pH changes are called local triggers. An extensive review on triggered release liposome has been published by Bibi *et al*.[22] Triggered release liposomal drug delivery is promising for future development in this sector of drug delivery systems although there is not much success has found yet. Product in preclinical stage showed promising effects against animal tumor model, but in clinical stage, it hampered by immune reaction in humans. Liver and spleen can be two parts to be targeted by liposome, and the effects of tumor tissue can be analyzed tomography. Liposome has also been a great application in transdermal drug delivery systems.

### Liposome in delivery of nucleic acids

Gene expression is observed in local than systemic area, although there are a number of cationic lipids have been synthesized recently, and after administering them, there were significant toxic side effects were observed.[23-25] It is evident that DNA or other nucleic acids conjugated with ligand-bearing liposome have shown significant increase in gene expression than non-targeted delivery of nucleic acids.[26] There are two types of vectors used in liposomal DNA delivery which are LPD-I and LPD-II (liposome-entrapped, polycation-condensed DNA). These two vectors are greatly versatile and safe vectors than other. Most recent applications of liposome are DNA vaccination and gene therapy to treat diseases caused by genetic deficiencies.

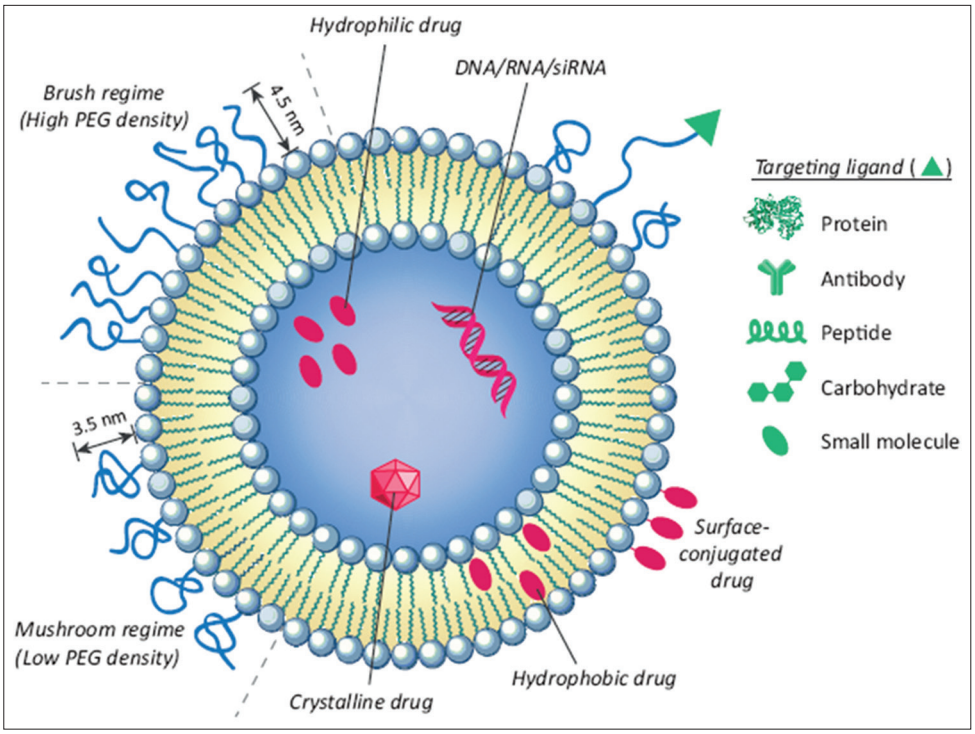


**Figure 1:** Structural features of liposomal drug delivery systems with entrapped molecule. Liposome can function through surface too to enhance receptor-mediated endocytosis by binding with ligands such as antibodies, proteins, and carbohydrates[13]

### Liposome in combination therapy

Combination therapy is used for the treatment to reduce toxic side effects of a single drug as well as to increase therapeutic efficacy of the combinations than individual drugs. As mainly the highly toxic drugs are used in combination so it will be a potential approach to deliver those drugs on targeted sites of action by liposome or nanomedicine.[27]

### Liposomal vaccine and antigen delivery system

The safety of the liposomal drug delivery system makes it a smart choice for mesenchymal stem cell-based therapy to deliver the viral gene. This is a preferred drug delivery for the vaccine and antigen because it has a lack of immunogenicity, minimal toxicity and can entrap large gene for delivery.[28] At a variety of diseases are treated with liposomal antigen delivery system. Vaccine and protein entrapped in liposome use various combinations of components like lipids surfactants and other solvent.[29] Liposomal drug delivery of vaccine is prepared by mixing various compounds like microbes to be vaccinated, antigen in soluble form, and cytokines from DNA and liposome. Antigens are usually covalently bonded to liposomal membrane.[30] Liposome in immunological therapy was first used for diphtheria toxoid to enhance immune response.[31]

### Liposome in cancer therapy

The main problem with the anticancer drugs is their low therapeutic index because of low therapeutic index normal dose of these which is needed for intended effect causes toxicity to normal cells. Targeted delivery of drugs to the tumor cells by liposome have been changed the pattern of cancer treatment. Due to the targeted delivery of toxic anticancer drugs, its toxicity has been reduced greatly than delivery of free anticancer drugs.[32-34] Entrapment of anticancer drugs greatly increased its lifetime, decreased its degradation rate, increased deposition in the tumor cells, and decreased uptake to the normal cells. Liposome with passively targeted tumor cells can increase vascular permeability.[35,36] Doxil, Caelyx, and Myocet are some commonly used liposomal formulation used in cancer treatment.[37,38]

## DISCUSSION

When the average diameters of liposome are in the ultrafilterable range (b200 nm), they can accumulate passively to the sites of increased vascular permeability for this accumulation and their reduced side effects liposomal drugs have been useful to clinical applications for the treatment of a wide range of diseases.[39] Vascular permeability can also be increased by hyperthermia. For triggered release of liposomal drugs, local hypothermia is used greatly with specific lipids, polymers, or other molecules.[40] Another new development of liposomal drug delivery is, their properties of specific binding to a target cell-like tumor cells or to a specific molecule such as antibodies and proteins. Some liposomes like stealth liposome are used to carry water soluble drugs like doxorubicin, mitoxantrone to achieve their maximum

effects.[41] Liposome can be used to target monocytes and macrophages, which are associated with various diseases like cancer, and atherosclerosis, therefore, targeting them with liposome are proven to be significant in recent times.[42]

Nanoparticles are precisely used in the treatment of prostate cancer and breast cancer cells that is why liposome incorporation with nanoparticles are used for the precise delivery of chemotherapeutic drugs to the cancerous cell which is a significant approach to treating cancer.[43]

## CONCLUSION

The pliability of liposomal drug delivery systems makes it useful for the delivery of a wide range of drugs through any route without concerning their solubility profile. It can prolong the action of drugs by gradually releasing to the target sites of applications. Not a single factor makes it successful as a vehicle in pharmaceutical sciences rather there are many factor to consider. In case of liposomal drug delivery system, drug distribution and drug releasing are not only regulated by drugs property but also depends on carrier molecule so that liposome can greatly affect the pharmacokinetics and pharmacodynamics profile of drugs. Liposome has created a new era in pharmaceutical drug delivery system with lots of opportunities for future.

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## REFERENCES

1. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol 1965;13:238-52.
2. Fielding RM. Liposomal drug delivery. Advantages and limitations from a clinical pharmacokinetic and therapeutic perspective. Clin Pharmacokinet 1991;21:155-64.
3. Akbarieh M, Besner JG, Galal A, Tawashi R. Liposomal delivery system for the targeting and controlled release of praziquantel. Drug Dev Ind Pharm 1992;18:303-17.
4. Gregoriadis G. Drug entrapment in liposomes. FEBS Lett 1973;36:292-6.
5. Gregoriadis G. The carrier potential of liposomes in biology and medicine (second of two parts). N Engl J Med 1976;295:765-70.
6. Alahari SK, DeLong R, Fisher MH, Dean NM, Viliet P, Juliano RL. Novel chemically modified oligonucleotides provide potent inhibition of P-glycoprotein expression. J Pharmacol Exp Ther 1998;286:419-28.
7. Kimelberg HK, Tracy TF Jr, Biddlecome SM, Bourke RS. The effect of entrapment in liposomes on the *in vivo* distribution of [3H] methotrexate in a primate. Cancer Res 1976;36:2949-57.
8. Poste G, Papahadjopoulos D. Lipid vesicles as carriers for introducing materials into cultured cells: Influence of vesicle lipid composition on mechanism (s) of vesicle incorporation into cells. Proc Natl Acad Sci 1976;73:1603-7.
9. Juliano RL, Stamp D. Pharmacokinetics of liposome-encapsulated anti-tumor drugs. Studies with vinblastine, actinomycin D, cytosine arabinoside, and daunomycin. Biochem Pharmacol 1978;27:21-7.
10. Sessa G, Weissmann G. Incorporation of lysozyme into liposomes. A model for structure-linked latency. J Biol Chem 1970;245:3295-301.
11. Mozafari MR. Liposomes: An overview of manufacturing techniques. Cell Mol Biol Lett 2005;10:711-9.
12. Gregoriadis G, Florence AT. Liposomes in drug delivery. Clinical, diagnostic and ophthalmic potential. Drugs 1993;45:15-28.
13. Noble GT, Stefanick JF, Ashley JD, Kiziltepe T, Bilgicer B. Ligand-targeted liposome design: Challenges and fundamental considerations. Trends Biotechnol 2014;32:32-45.
14. Semalty A, Semalty M, Rawat BS, Singh D, Rawat MS. Development and evaluation of pharmacosomes of aceclofenac. Indian J Pharm Sci 2010;72:576-81.
15. Shivhare R, Pathak A, Shrivastava N, Singh C, Tiwari G, Goyal R. An update review on novel advanced ocular drug delivery system. World J Pharm Pharm Sci 2012;1:545-68.
16. Leserman LD, Weinstein JN, Blumenthal R, Terry WD. Receptor-mediated endocytosis of antibody-opsonized liposomes by tumor cells. Proc Natl Acad Sci U S A 1980;77:4089-93.
17. Straubinger RM, Hong K, Friend DS, Papahadjopoulos D. Endocytosis of liposomes and intracellular fate of encapsulated molecules: Encounter with a low pH compartment after internalization in coated vesicles. Cell 1983;32:1069-79.
18. Heath TD, Montgomery JA, Piper JR, Papahadjopoulos D. Antibody-targeted liposomes: Increase in specific toxicity of methotrexate-gamma-aspartate. Proc Natl Acad Sci U S A 1983;80:1377-81.
19. Riviere K, Huang Z, Jerger K, Macaraeg N, Szoka FC Jr. Antitumor effect of folate-targeted liposomal doxorubicin in KB tumor-bearing mice after intravenous administration. J Drug Target 2011;19:14-24.
20. Charrois GJ, Allen TM. Rate of biodistribution of STEALTH liposomes to tumor and skin: Influence of liposome diameter and implications for toxicity and therapeutic activity. Biochim Biophys Acta 2003;1609:102-8.
21. Dreher MR, Liu W, Michelich CR, Dewhirst MW, Yuan F, Chilkoti A. Tumor vascular permeability, accumulation, and penetration of macromolecular drug carriers. J Natl

Cancer Inst 2006;98:335-44.
22. Bibi S, Lattmann E, Mohammed AR, Perrie Y. Trigger release liposome systems: Local and remote controlled delivery? J Microencapsul 2012;29:262-76.
23. Mok KW, Cullis PR. Structural and fusogenic properties of cationic liposomes in the presence of plasmid DNA. Biophys J 1997;73:2534-45.
24. Hirko A, Tang F, Hughes JA. Cationic lipid vectors for plasmid DNA delivery. Curr Med Chem 2003;10:1185-93.
25. Filion MC, Phillips NC. Toxicity and immunomodulatory activity of liposomal vectors formulated with cationic lipids toward immune effector cells. Biochim Biophys Acta 1997;1329:345-56.
26. Wang S, Lee RJ, Cauchon G, Gorenstein DG, Low PS. Delivery of antisense oligodeoxyribonucleotides against the human epidermal growth factor receptor into cultured KB cells with liposomes conjugated to folate via polyethylene glycol. Proc Natl Acad Sci U S A 1995;92:3318-22.
27. Pastorino F, Brignole C, Di Paolo D, Nico B, Pezzolo A, Marimpietri D, *et al.* Targeting liposomal chemotherapy via both tumor cell-specific and tumor vasculature-specific ligands potentiates therapeutic efficacy. Cancer Res 2006;66:10073-82.
28. Madeira C, Mendes RD, Ribeiro SC, Boura JS, Aires-Barros MR, da Silva CL, *et al.* Nonviral gene delivery to mesenchymal stem cells using cationic liposomes for gene and cell therapy. J Biomed Biotechnol 2010;2010:735349.
29. Shilpa S, Srinivasan BP, Chauhan M. Niosomes as vesicular carriers for delivery of proteins and biologicals. Int J Drug Deliv 2011;3:14-24.
30. Wassef NM, Alving CR, Richards RL. Liposomes as carriers for vaccines. Immunomethods 1994;4:217-22.
31. Allison AG, Gregoriadis G. Liposomes as immunological adjuvants. Nature 1974;252:252.
32. Gregoriadis G. Engineering liposomes for drug delivery: Progress and problems. Trends Biotechnol 1995;13:527-37.
33. Gregoriadis G. Liposomes as Drug Carriers: Recent Trends and Progress. Chichester: Wiley; 1988. p. 3-18.
34. Lasic DD, Papahadjopoulos D. Medical Applications of Liposomes. Amsterdam: Elsevier; 1988.
35. Gabizon AA. Selective tumor localization and improved therapeutic index of anthracyclines encapsulated in long-circulating liposomes. Cancer Res 1992;52:891-6.
36. Mayer LD, Reamer J, Bally MB. Intravenous pretreatment with empty pH gradient liposomes alters the pharmacokinetics and toxicity of doxorubicin through *in vivo* active drug encapsulation. J Pharm Sci 1999;88:96-102.
37. Taneja D, Namdeo A, Mishra PR, Khopade AJ, Jain NK. High-entrapment liposomes for 6-mercaptopurine-a prodrug approach. Drug Dev Ind Pharm 2000;26:1315-9.
38. Hassan M, Hassan Z, Nilsson C, Rehim MA, Kumlien S, Elfsson B, *et al.* Pharmacokinetics and distribution of liposomal busulfan in the rat: A new formulation for intravenous administration. Cancer Chemother Pharmacol 1998;42:471-8.
39. Allen TM, Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. Adv Drug Deliv Rev 2013;65:36-48.
40. Ponce AM, Vujaskovic Z, Yuan F, Needham D, Dewhirst MW. Hyperthermia mediated liposomal drug delivery. Int J Hyperthermia 2006;22:205-13.
41. Samad A, Sultana Y, Aqil M. Liposomal drug delivery systems: An update review. Curr Drug Deliv 2007;4:297-305.
42. Kelly C, Jefferies C, Cryan SA. Targeted liposomal drug delivery to monocytes and macrophages. J Drug Deliv 2011;2011:727241.
43. Malam Y, Loizidou M, Seifalian AM. Liposomes and nanoparticles: Nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci 2009;30:592-9.

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