AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Review on Topical Liposome: Drug Delivery Through Skin

Gitanjali Shivaji Bhatjire[1*], Santosh Dattu Navale [1], Kishor Sahebrao Salunkhe[1]
1.Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner 422605, India

ABSTRACT

Liposome proved themselves as a promising novel delivery vehicle of drugs to the skin, is a topic of considerable current interest. Liposomes are acceptable and superior carriers having ability to encapsulate both hydrophilic and lipophilic drugs and protect them from degradation. Liposomes are result of self-assembly of phospholipid in an aqueous media resulting in closed bilayer structures. Liposomes are one of unique drug delivery system which can be used in controlling and targeting drug delivery system. Liposomes are generally classified based upon structure, method of preparation, composition and application, conventional liposome, and specialty liposome. Different marketed formulations are available in market for liposomes. The liposomes have many applications which increase its importance over other formulations. The entrapped compound's solubility and partitioning characteristics will determine its location in the liposomal bilayer .It also has affinity to keratin of horny layer of skin and can penetrate deeper into skin hence give better absorption. But they may also have the property into the skin, carrying actives to the target site, where these molecules will be released. Reformulation of drugs in liposomes has provided an opportunity to enhance the therapeutic indices of various agents. This review discusses the potential advantages in topical drug delivery, basic structure characteristics and mechanism of action of liposomes and evaluation parameter for liposome formulation.

Keywords: Liposome, penetration, skin, enhanced efficiency.

*Corresponding Author Email: gitsbhatjire88@gmail.com
Received 08 April 2017, Accepted 17 April 2017

Please cite this article as: Bhatjire GS *et al*., Review on Topical Liposome: Drug Delivery Through Skin**.** American Journal of PharmTech Research 2017.

INTRODUCTION

Liposomes are artificially prepared vesicles made of lipid bilayer. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes can be prepared by disrupting biological membrane, for example by sonication. Liposomes are micro particulate or colloidal carriers usually 0.05-5.0 µm in diameter which form spontaneously when certain lipid are hydrated in aqueous media. Liposomes are composed of relatively biocompatible and biodegradable material, and they consists of an aqueous volume entrapped by one or more bilayer of natural and/or synthetic lipids, drug with widely varying lipophilicities can be encapsulated in liposomes, either in the entrapped aqueous volume or at the bilayer interface. The name liposome is derived from two Greek words 'lipos' meaning fat and 'soma' meaning body. A liposome can be formed at a variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids and not to its size. Because of their biocompatibility, biodegradability, low toxicity, and aptitude to trap both hydrophilic and lipophilic drugs and simplify site specific drug delivery to tumor tissues. Liposomes have increased rate both as an investigational system and commercially as a drug delivery system. Many studies have been conducted on liposomes with the goal of decreasing drug toxicity and/or targeting specific cells. The application of Liposomes in skin treatment is based on the convenience that the spherical vesicles may encapsulate a wide range of active ingredients. Furthermore, the bilayer structure of lipid vesicles has similarity to that of cellular membranes. As a result of this similarity, the liposomes are able to interact with the cutaneous cells in different ways, such as endocytosis, fusion, or exchange of lipids. The latter has a specific impact in topical preparations and dermocosmetics, since it may alter the physical properties of the skin. [3, 4, 14]

Advantages5, [7, 13]

1. 1.Liposomeis biocompatible, completely biodegradable, non-toxic in nature.
2. They are suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs.
3. They protect the encapsulated drug from external environment.
4. They reduce toxicity and increase stability since therapeutic activity of chemotherapeutic agent can be improved through liposome encapsulation. This reduces deleterious effects that are observed at concentration similar to or lower than those required for maximum therapeutic activity.
5. It reduces exposure of sensitive tissue to toxic drugs.

6. They are similar to the epidermis with respect to their lipid composition which enables them to penetrate the epidermal barrier to a greater extent compared to other dosage forms.
7. Alter the pharmacokinetic and pharmacodynamic property of drugs(reduce elimination, increased circulation life time).
8. Provides selective passive targeting to tumor tissue (liposomal doxorubicin).
9. Liposome is increased stability via encapsulation. Liposomes are biocompatible, completely biodegradable, non-toxic, flexible and non immunogenic for systemic and non-systemic administrations.

Disadvantages [5, 13]

1. Liposome's production cost is high.
2. Leakage and fusion of encapsulated drug/ molecule can occur.
1. It has short half life in reticuloendothelial system, particularly the kuffer cells in the liver remove liposome from the circulation.
2. They are prone to degradation by oxidation and hydrolysis.
3. Less stable. The development of liposomes at industrial level is difficult due to its physiological and physicochemical instability.

SKIN[6, 9]

The Structure of the Skin

The skin consists of the epidermis and the dermis, which sits on a layer of subcutaneous fat. The epidermis contains four histologically distinct layers, from the innermost stratum basal via the stratum spinosum and stratum granulosum (SG) to the superficial stratum corneum (SC). The SC has been represented as a brick and mortar structure in which the corneocytes are embedded in an intercellular lipid matrix. The corneocytes comprise insoluble keratins enveloped by cross- linked proteins, and are arranged in parallel, overlapping, multicellular stacks perpendicular to the skin surface. The inter-corneocytes space is filled with lipids, usually present in the crystalline phase. Most SC lipids are synthesized in the viable epidermis during differentiation; they are released into the intercellular spaces at the SG-SC interface. From lamellar bodies. The major SC lipids are ceramides, fatty acids and cholesterol.

The skin is the largest organ in the human body weight, contributing about 10% of total weight and covering an average area of 1.7 m^2 it regulates water and heat loss, and prevents the invasion of noxious chemicals and microorganisms. Because skin is an easily accessible organ, its potential as an alternative route for administrating drugs for both systemic and local effect has attracted considerable interest. However, molecules do not easily penetrate the skin because of its excellent

barrier function. As a result, various nano carriers have been developed in an attempt to reversibly modulate the skin barrier and/or provide novel delivery systems for the active of interest. These particulate carriers include nano emulsion, liposomes, solid lipid nanoparticles, niosomes etc. The ability of the stratum corneum to act as a reservoir for drug transport through the skin was amply demonstrated by Rougier et.al, who reported that the absorption of a variety of drugs through the skin was proportional to the amount of drug recovered in the stratum corneum following 30 min topical application. It is therefore important to examine the extent of drug accumulation in the various strata of the skin in addition to estimating percutaneous absorption profiles. A common procedure for the determination of drug levels in the skin strata involves stripping of treated skin with adhesive tape. With the use of appropriately radiolabeled drugs and liposomal lipids, it has been possible to obtain both drug and liposomal lipid distributions in the various strata of the skin

Why there is any need for liposomes as new drug carrier systems with topical dermatics?[7]

The major problem concerning the efficacy of topicaldrug is that they have to reach the site of action and to stay there in an effective concentration for a certain time. Although the skin belongs to the organs which can be reached directly drug application on the skin surface does not automatically mean the drug getting to the right site of action. This in fact is the problem with the conventional dosage forms like creams and ointments. The use of penetration enhancers, e.g. dimethylsulphoxide (DMSO) or propylene glycol leads, on the one hand, to an improved transport rate through the epidermal barrier but, on the other to more unwanted effects due to an increases systemic drug level. Moreover irritative or even toxic side effects are reported leading to the conclusion that addition of penetration enhancers does not really mean an improvement in topical drug administration.

Pharmacokinetics of Liposomes[13]

1. Liposomal drug can be applied through various routes, but mainly IV and topical administration is preferred. After reaching in the systemic circulation or in the local area, a liposome can interact with the cell by any of the following methods.
2. Endocytosis by phagocytotic cells of the R.E.S. such as macrophages and neutrophils.
3. Adsorption to the cell surface either by non specific weak hydrophobic or electrostatic forces or by specific interaction with cell surface components.
4. Fusion with the plasma cell membrane by insertion of lipid bilayer of liposome into plasma membrane with simultaneous release of liposomal contents into the cytoplasm.
5. Transfer of liposomal lipids to cellular or sub cellular membrane or vice versa without any association of the liposomal content.

6. It is often difficult to determine what mechanism is operative and more than. One may operate at the same time

MECHANISM OF ACTION[8]

A liposomal formulation to be effective, especially for hydrophilic drugs, it is essential that the suspension undergo significant dehydration. Since in most studies reported the lipid concentration scarcely exceeds 100mg/ml, the bulk aqueous medium constitutes roughly 90% of the formulation. Thus without a high degree of dehydration, no advantages over simple aqueous solution can be governed by employing liposomal systems, especially, if the drug action is anticipated to occur within few house after application. The dehydration of liposomal suspension can either be complete or reach an equilibrium stage wherein a certain amount of water is always held within the bilayers.

Transfer of hydrophobic drugs

A major fraction of the added drug would be encapsulated or intercalated within the lipid bilayers of the liposomes. Further, optimum loading of hydrophobic drugs would be possible only if the lipid bilayers are maintained above the Tm of the major lipid the transfer of drug from lipid bilayers into skin can occur as long as the bilayer are in liquid crystalline state. If the liquid crystalline phase is altered to the gel state, transport of the drug will cease or be negligibly low. Thus, the extent of dehydration will determine if changes in the state of the liposomal bilayers from a liquid crystalline phase to the gel state are possible. A second consequence of dehydration involves the formation of a strong adhesive patch of liposomal bilayer on the skin.

Transfer of hydrophilic drugs

The mode of action for liposomal transport of hydrophilic drugs parallels that for hydrophobic drug in qualitative manner. This is strictly because of major role of the water associated with the bilayers upon dehydration of the liposomal suspension. Thus for liposomal systems that retain a constant amount of water within the bilayers following dehydration to an equilibrium state, drug transport would continue over extended periods of time.

The follicular option[7]

The mechanism described above occurs regardless of the presence or absence of follicles in the skin specimen however, when a follicular pathway is available, upon dehydration the liposomal bilayers can partition and pack into the follicular or hair ducts. This partitioning is favorable since the follicular ducts contain lipids. The filling of the follicular opening with the liposomal bilayers not only results in entrapped drugs being carried into the follicles but also allows partitioning of unentrapped drugs into the bilayer matrix within follicles.

General Method of Preparation of Liposome[10]

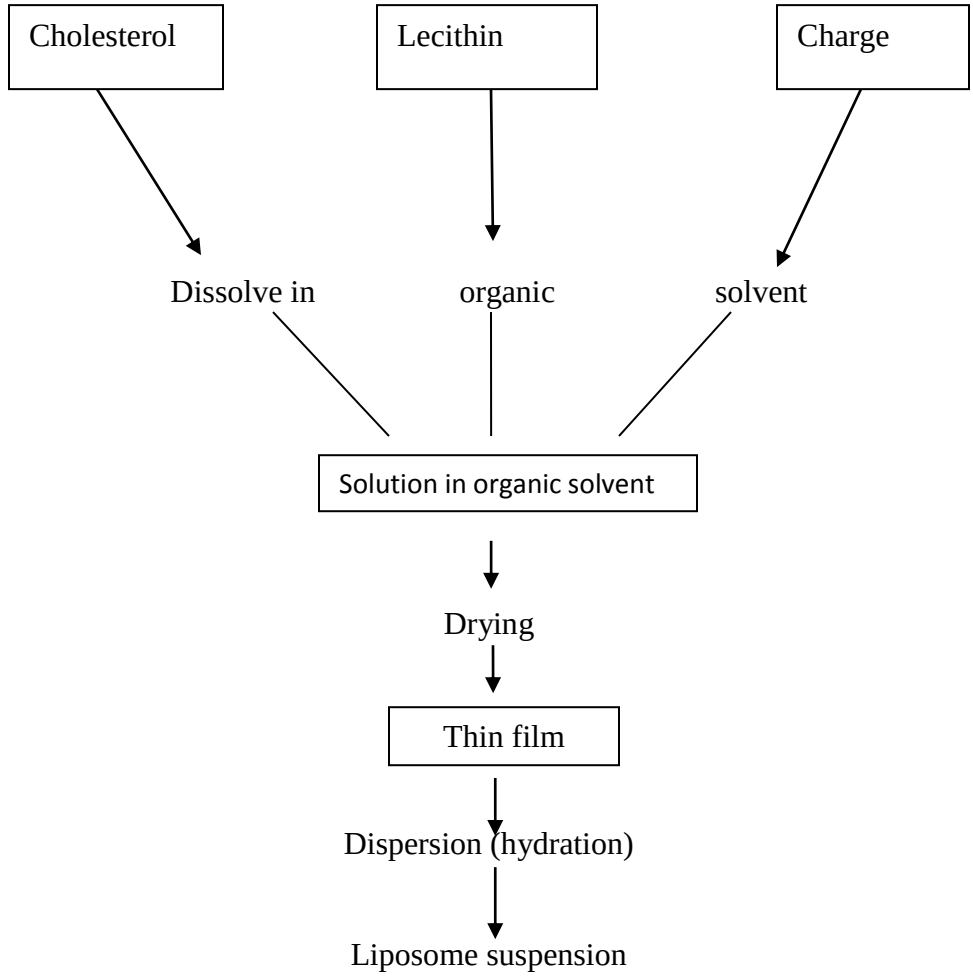

Figure 1: General method of preparation of liposome

Liposomes are manufactured in majority using various procedures in which the water soluble (hydrophilic) materials are entrapped by using aqueous solution of these materials as hydrating fluid or by the addition of drug/ drug solution at some stage during manufacturing of the liposomes. The lipid soluble (lipophilic) materials are solubilized in the organic solution of the constitutive lipid and they evaporated to a dry drug containing lipid film followed by its hydration. These methods involve the loading of the entrapped agents before or during the manufacturing procedure (passive loading).

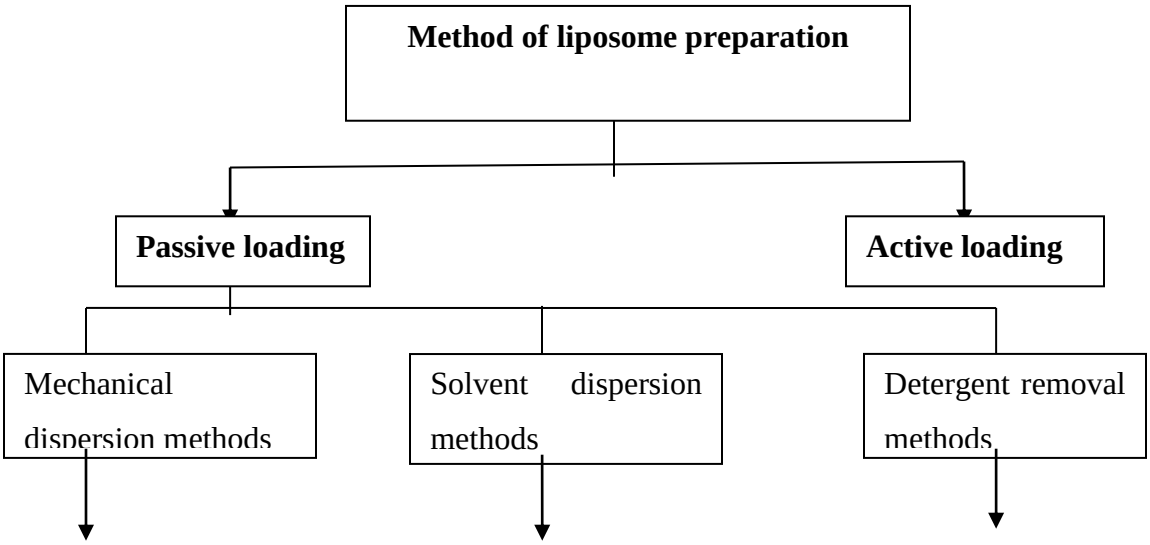

Figure 2: **Method of Liposome Preparation**

Evaluation[8, 11, 12, 1]

Size and Size distribution

Prepared liposomal batches were monitored for their morphological attributes using optical microscope. Mean vesicle size and size distribution profile of liposome was determined by using Malvern particle size analyzer model SM2000, which follows Mie's theory of light scattering. Diluted liposome suspension was added to the sample dispersion unit containing stirrer and stirred at 2000 rpm in order to reduce the interparticle aggregation, and laser obscuration range was maintained between 10-20%.The average particle size was measured after performing the experiment in triplicate.

Zeta potential analysis

The significance of zeta potential is that its value can be related to the stability of colloidal dispersions. So, colloids with high zeta potential (negative or positive) are electrically stabilized while colloids with low zeta potentials tend to coagulate or flocculate. A value of 25 mV(positive or negative) can be as the arbitrary value that separates low charged surfaces from high charged surfaces. The zeta potential was analyzed by MALVERN ZETASIZER.

Storage –stability studies

The ability of vesicles to retain the drug (i.e. drug retentive behavior) was assessed by keeping the liposomal suspension at different temperature conditions, i.e. 4-5^{0}c (Refrigerator; RF), 25±2^{o}c (Room temperature; RT) and 37±2^{0}c for a period of 8 weeks. The liposomal suspension was kept in sealed vials (20 ml capacity) after flushing with nitrogen. Samples were withdrawn periodically and analyzed for drug content, in the manner described under drug entrapment studies.

Entrapment efficiency

Drug associated with liposome was separated from unentrapped drug using centrifugation method. Liposomes were centrifuged at 2000 rpm for 1 hr at controlled temperature of 4^0 c. supernatant containing unentrapped drug was withdrawn and measured UV spectrometrically against phosphate buffer saline (PH 7.4). The amount of drug entrapped in liposome was determined as follows.

$$\mathbf{EE\% = [Cd\text{-}Cf/Cd] \times 100}$$

Where, Cd is concentration detected of total drug and Cf is concentration of free drug. The entrapment efficiency was obtained by repeating experiment in triplicate and the values were expressed as a mean standard deviation.

In-vitro skin permeation study

Skin permeation studies with liposome formulation were carried out using hairless abdominal skin of Wister rat, employing modified Franz diffusion cells. The results obtained were compared with that of no-liposomal formulation of drug.

Table 1: Target allowing with Drug as Liposomal Drug Delivery[17]

Sr no	Drugs	Marketed	Type of liposome	Target	Development stage
1	Cyclophosphamide	Cytoxan inj. (No longer in market)	-	Lung cancer	NA
2	Docetaxel Anhydrous	Taxotere	Long- circulating	Breast cancer	Phase I
3	Doxorubicin	Mycoset Doxil, Caelix	Non-PEGylated PEGylated	Breast cancer Caposis sarcoma,	Phase-III
4	Paclitaxel	LEP-ETU, Taxol, Abraxane	PEGylated	Breast cancer	Phase II
5	Pemetaxel, Cisplatin	Alimta	PEGylated	Head and neck cancer	Trial
6	Bendumustine Hcl	Trenda	Long- circulating	Brest cancer	Phase I

CONCLUSION

Liposomes show some advantages which make them look interesting as drug carriers for topically applied drugs. The topically applied liposomal formulations, particularly those prepared from lipid mixtures of composition similar to the stratum corneum would be an effective delivery system for the treatment of skin diseases. Since these liposomal formulations provide sustained, enhanced levels in deeper strata of the skin, they have the capacity to meter a sufficient quantity of drug into deeper tissue to treat the skin symptomatology [7].

ACKNOWLEDGMENT

I would like to thanks Amrutvahini College of pharmacy, Sangamner, India for continuous support and encouragement throughout this review work

REFERENCES

1. Nikhil AS et al,Topical liposomal gel: a novel drug delivery system, Int J Res Pharm Chem 2012: 2: 383
2. Loveleenpreet K, Prabhjot K, Khan MU, and Liposome as a drug carrier: a review, Int J Res Phar Chem 2013: 3(1): 121
3. Mansoori ML, Agrawal S, Jawades, Khan MI, Review on Liposome, Int J Adv Res Pharm and Bio Sci, 2012 4(2) 453-454
4. Saraswathi M, Umasankar K, Jayachandra P, A review on Liposome, Int J Res Pharm and Nano Sci:2014: 3 (3):159-169
5. Deepthi V, Kavitha AN, Liposomal drug delivery system, RGUHS J Pharm Sci: 2014:2(4):48-49
6. Egbaria K, Weiner N, liposomes as a topical drug delivery system, Advance drug delivery reviews, Elsevier: 1990:5 287-300
7. Patel MC, Patel HK, Suthar RM, Patel SR, Liposome as a topical drug delivery system, Int J Pharm and Chem Sci: 2012:1 (1): 3-5
8. Rathore A, Jatr C., Sharma N, Tiwari R, Farheen F, Sharma G, A review on liposomes as a topical drug delivery , Indo Am J Pharm Res 2013: 3427-3429
9. Xiao WU, Richard H, Application of Nanoparticles in Topical Drug Delivery and In Cosmetics, J of Drug Delivery Sci and Tech: 19(6): 371-384
10. Dual JS, Rana AC, and Bhandari AK, Liposome: Methods Of Preparation And Application, IntJ Pharm Stu and Res: 2012: 2(3): 14-20

11. Purushothaman M, Viswanath V, Narashimha BR, Irshud B, Preparation and evaluation of decitabine liposomes, Indo Ame J Pharm Sci 2015: 2(9): 1264-1273
12. Patel SS, Patel MS, Salampure S, Vishwanath B, and Patel NM, Development and Evaluation of Liposomes for Topical Delivery of Tacrolimus, J. Sci Res 2010:2(3) :585-596
13. Chandraprakash D, PrashantL, ShikhaR, Rajn Y, S Prakash Liposome: A Powerful Approach For Vesicular Drug Delivery System World J Pharm Res:1(4):1110-1141.
14. 14 Livia B, Nora K, Pal G, Katalin L, Liposomes for atopical use: a physic chemical comparison of vesicles prepared from egg or soy lecithin, Sci Pharm 2013: 81: 1151-1166
15. Chauhan T, Arora S, Parashar B , Chandel A, Liposome drug delivery: A review, Int J Pharm and Chem Sci: 20123 (1): 1103
16. Gabriele B et.al, flexible liposomes for topical application in cosmetics, Research gate, Oct-2016:2-3
17. Navale SD, Salunkhe KS, and Harwalkar MS, A Review on Liposome: The Cancer Targeting Aspects and Effective Upgraded Vesicular Systems, Am J Pharm Tech Res, 2017:7 (2): 492