Review Article

Liposomes: As A Topical Drug Delivery System

Patel Meghana C[1]*, Patel Hardik K[2], Suthar Rajnikant M[2] and Patel Sandip R[2]

[1]Mehsana Urban Bank Institute of Biosciences, Ganpat University, Kherva, Gujarat, India.
[2]A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar, Anand, Gujarat, India.

_____

ABSTRACT
Liposomes are simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecule. There are a number of components present in liposomes, with phospholipid and cholesterol being the main ingredients. The type of phospholipids includes phosphoglycerides and sphingolipids, and together with their hydrolysis products. Classification of liposomes is based on lamellae and composition and on the basis of size and number of lamellae. In this article basic characteristic, marketed formulation and future prospectus of liposomes are discussed.

Keywords: Liposomes, Penetration, Lamellae, Controlled release, Drug retention.

INTRODUCTION

Liposomes are microscopic vesicles composed of one or more lipid bilayers arranged in concentric fashion enclosing an equal number of aqueous compartments. Various amphipathic molecules have been used to form the liposomes and the method of preparation can be tailored to control their size and morphology. Drug molecules can either be encapsulated in the aqueous space or intercalated into the lipid bilayer; the exact location of a drug in the liposome will depend upon its physicochemical characteristics and the composition of the lipids.[1-4]

Liposomes, i.e., phospholipid vesicles, are widely applied for the topical treatments of diseases in dermatology. Many drugs encapsulated into liposomes show enhanced skin penetration. Because of their ability to provide a sustained and controlled release of the incorporated material, liposomes also have a potential for being applied vaginally. The major disadvantage of using liposomes topically and vaginally lies in the liquid nature of the preparation. To achieve the viscosity desirable for application, liposomes should be incorporated into a suitable vehicle. It has been well established that liposomes are fairly compatible with viscosity increasing agents (methylcellulose) and polyacrylic acid (Carbopol).[5,6]

Several techniques have been explored to increase the drug penetration rate across skin including iontophoresis and penetration enhancement, particularly for the delivery of peptides and proteins. Here focus on a third alternative method, the encapsulation of drugs in lipid vesicles prepared from phospholipids (liposomes) which have been shown to facilitate transport of drugs into and across skin. While liposomes have been investigated for many years as parenteral drug carrier systems, particularly for the selective delivery of anticancer, antibiotic and antifungal agents, they have only for approximately one decade been considered for topical drug delivery, including ophthalmic, pulmonary and dermal/ transdermal delivery.[7-9]

Due to their high degree of biocompatibility, liposomes were initially conceived of as delivery systems for intravenous delivery. It has since become apparent that liposomes can also be useful for delivery of drugs by other routes of administration. Liposomes are frequently used as vehicles in pharmaceuticals and cosmetics for a controlled and optimized delivery to particular skin layers. Liposomes are spherical vesicles whose membrane

consists of amphiphilic lipids (i.e., lipids that are hydrophilic on one side and lipophilic on the other side) that enclose an aqueous core, similar to the bilayer membranes of living cells. Because liposomes offer an amphiphilic environment, they may encapsulate hydrophilic substances in their aqueous core and lipophilic substances in their lipid bilayer. This unique dual release capability enables the delivery of 2 types of substances once they are applied on the skin; each differs in its effects on skin permeability, which may enhance the desired therapeutic benefit.[1]

Structure and Composition of Liposome

Among the variety of new drug delivery systems. liposomes seem to have the best potential to accommodate both water and lipid soluble compounds. to protect the liposome-encapsulated drug from metabolic degradation and to act as a delivery mechanism, releasing active ingredients slowly and in a controlled manner.

Phospholipids, the comerstone of the liposome lipid bilayer. usually extracted from egg yolk or soy bean oil consist of a hydrophilic head portion covalently attached to two hydrocarbon tails representing the lipophilic portion. Aggregation in a bilayer structure occurs by orientation of the hydrophilic head groups towards the aqueous environment. While keeping the lipophilic hydrocarbon chains sequestered inside. Formation of such a configuration provides the vesicle with the lowest potential energy state through solvation of the polar head groups and hydrophobic interactions of the lipid chain.[10, 11]

Natural phosphatidylcholine extracted from egg yolk or soy bean oil or its semisynthetic derivatives represents the main constituent in various liposomal formulations. The chemical structure of naturally occurring phosphatidylcholine has a glycerol moiety attached to two acyl chains which may be saturated or unsaturated. Each may have between 10 to 24 carbon atoms. together forming the hydrophobie (lipophilic) portion of the molecule. The charged phosphate and choline moieties form the hydrophilic "head".

The fatty acid chains, depending on their length and degree of saturation, can exist in the gel phase in which the lipids are rigid, impermeable and easily aggregated upon storage or in the more fluid liquid-crystailine phase. The temperature at which the gel phase converts to the liquid-crystalline phase is known as the transition temperature. Cholesterol is frequently added in minute quantities to most liposomal formulations to increase the fluidity of the liposomal gel phase enhance the retention of hydrophilic particles and to stabilize the bilayer membrane in a manner similar to that of biological membranes.[10, 12]
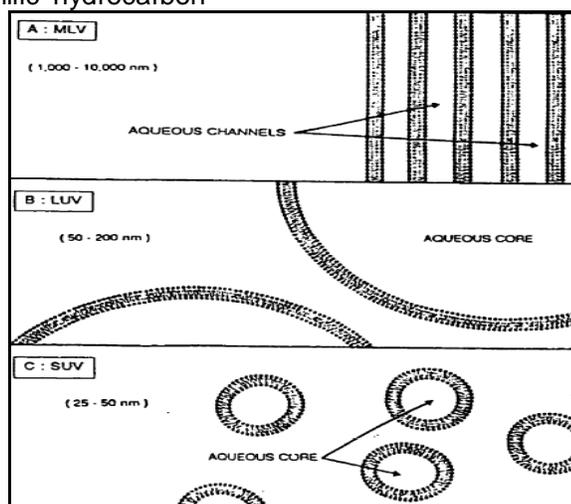

Fig. 1: A diagrammatic representation of three main class of liposomes.
(A) Multilamellar vesicles; (B) Large unilamellar vesicles; (C) Small unilamellar vesicles

Classification of Liposomes

Table I: Classification of liposomes based on size and lamellarity[13]

MLV	Multilamellar large vesicles	(>0.5 µm)
OLV	Oligolamellar vesicles	(0.1–1 µm)
UV	Unilamellar vesicles	(all sizes)
SUV	Small unilamellar vesicles	(20–100 nm)
MUV	Medium-sized unilamellar vesicles	-
LUV	Large unilamellar vesicles	(>100 nm)
GUV	Giant unilamellar vesicles	(>1 µm)
MVV	Multivesicular vesicles	(usually >1 µm)

Table II: Based on Method of Liposome preparation[10, 13]

REV	Single or Oligolamellar vesicles made by Reverse phase Evaporation method
MLV-REV	Multilamellar vesicles made by Reverse phase Evaporation method
SPLV	Stable plurilamellar vesicles
FATMLV	Frozen and Thawed MLV
VET	Vesicles prepared by extrusion technique
DRV	Dehydration-Rehydration Method

Advantage of Topical Liposome

Why is there any need for new drug carrier systems with topical dermatics?

The major problem concerning the efficacy of topical drugs 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 increased 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.[1,14]

What are the advantages of liposomes as drug carrier systems?

1. Similar to biological membranes they can store water-soluble and lipophilic substances in their different phases i.e. it readily incorporate a wide variety of hydrophilic and hydrophobic drugs.

2. 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.

3. According to studies performed so far liposomes are biodegradable and non-toxic which is important to avoid side effects.[3]

4. The really new aspect with liposomes is that they are thought to act as "drug localizers" - not only as "drug transporters". i.e. to enhance significantly the accumulation of drug at the site of administration as a result of the high substantivity of liposomes with biological membranes.

5. The uptake of intact liposomes by the reconstructed epidermis, these vesicles do not penetrate through healthy skin. Yet, this is to be expected in diseased skin without intact epidermal barrier. This is especially important as far as drugs like glucocorticosteroids or

retinoids are concerned which are known to create severe systemic effects when absorbed percutaneously to a greater extent. Vehicles which can transport these drugs to the wanted site of action within the skin would thus prevent systemic absorption and consecutively unwanted effects. This is the reason why liposomes as a promising form for topical drug delivery.

6. Liposome may serve as a local depot for the sustained release of dermally active compounds including antibiotics, corticosteroids or retinoic acid.

7. By virtue of penetration of individual phospholipid molecules or nonionic ether surfactants into the lipid layers of the stratum corneum and epidermis they may serve as penetration enhancer and facilitate dermal delivery leading to higher localized drug concentrations.[1,15]

Mechanism of Action of Topical Liposome

The mode by which liposome facilitate transfer of drug into living skin strata and beyond has been a topic of much interest. They propose a simple hypothesis of liposomal action that accounts for a majority of the effects observed. For 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 100 mg/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 hours 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.

Two interdependent factors control the extent of dehydration of a liposomal suspension.

1. The first is the phase transition temperature(Tm).
2. The second, often one that affects Tm, is the presence of components that either affect bilayer packing (e.g. cholesterol) or those that are humectants/cyroprotectants, such a hydrophilic polymers or glycerol and sugars.

The combined effect of the two factors will determine how much water will be retained by the liposomal bilayers following dehydration under non-occluded conditions. In the absence of enhancer effects arising out of the action of lipid components of the liposomal bilayers on skin, the extent and rate of dehydration of the liposomal bilayers control the extent and rate of transfer of drug, regardless of whether it is hydrophobic or hydrophilic, into skin.[16]

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 the lipid bilayers into skin can occur as long as the bilayers are in a liquid crystalline state. If the liquid crystalline phase is altered to the gel state, transport of the drug will cease or be negligibly low. Dehydration of liposomal suspensions has been shown to induce transitions from the liquid crystalline phase to the gel state. 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. If dehydration is complete and the bilayers are transformed from the liquid crystalline state to the gel state, then transfer of drug from the bilayer to the skin ceases. If dehydration to an equilibrium stage wherein a constant amount of water is always retained in the bilayers occurs, then transport of drug would be continues and steady. A second consequence of dehydration involves the

formation of a strong adhesive patch of liposomal bilayer on the skin. The formation of such patches maximizes the intimacy of contact between the drug - laden bilayer and the skin and probably is medicated via calcium bridges.[16]

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 slate, drug transport would continue over extended periods of time. A major consequence of dehydration for hydrophilic drugs involves the enhancement or enrichment of drug concentration in the aqueous phase of the bilayers leading to an enhancement in flux of drug into and across skin.[16]

The Follicular option

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.[16]

Method of Preparation of Liposome

Method of preparation of Liposome
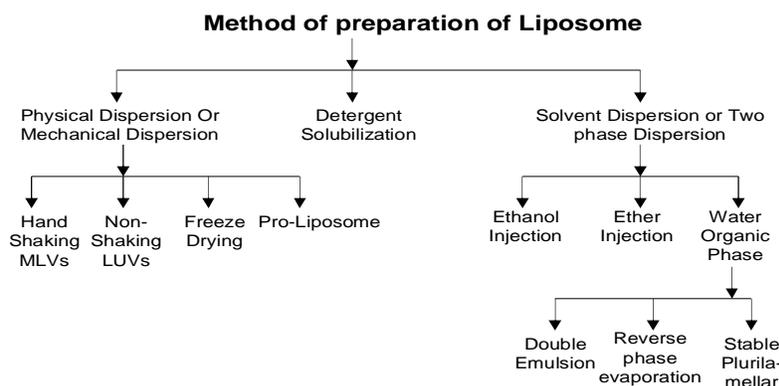
Processing Of Liposme Hydrated By Physical means
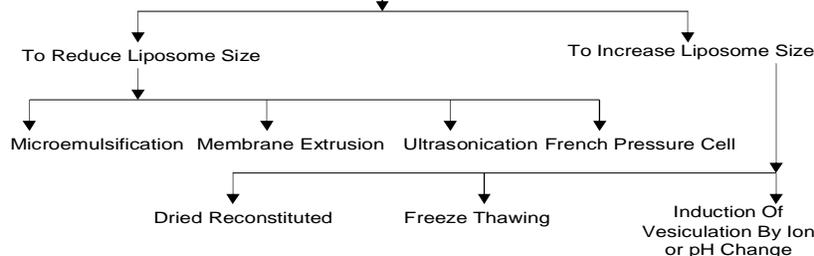
A pre-requisite to the successful development of liposome products is the capability to scale-up production methods at acceptable costs using processes that provide a high degree of reproducibility required for the finished products.[10, 17]

One of the most frequently used methods, originally described by Bangham is thin film hydration. Here a mixture of lipids dissolved in a volatile organic solvent is deposited as a thin film on the surface of a round bottom flask as the solvent is removed under reduced pressure by rotary evaporation. The MLVs will form spontaneously when an excess volume of aqueous buffer is added to the dry lipid and the flask is hand shaken vigorously.

Pro-liposome method, increase the surface area of dried lipid film by drying the lipid over finely devided particulate support, such as powdered sodium chloride, or sorbitol, or other polysaccharides. These dried lipid coated particulate are called pro-liposome.[17]

Injection of a water-immiscible solvent such as ether containing a mixture of bilayer-foming lipids into an aqueous medium at 55- 65 °C or under reduced pressure will form single layer vesicles with diameters ranging fiom 50-200 nm upon evaporation of the ether.[18]

The reverse phase evaporation technique is another method designed to form LUVs. A water-in-oil emulsion of phospholipids and buffer in an excess of organic phase is sonicated followed by removal of the organic phase under vacuum. Removal of the last traces of solvent transforms the emulsion from the gel state into large unilamellar vesicles.[19]

LUVs can be produced fiom a mixture of MLVs using high pressure extrusion. After repeated extrusion through polycarbonate membrane with uniform pores of selected sizes (80-400 nm), under high pressure (up to 800 psi), liposomes with the desired average diameter will be formed.[19]

Purification of Liposomes

Liposomes are commonly purified by either gel filtration column chromatography or by dilysis or centrifugation. In column chromatographic separation Sephadex G-50 is most widely used material. In this column chromatographic separation liposome membrane may bind or interactwith the surface of the polydextran beads. There may be small amount of lipid lost resulting into destabilization of the membrane leading to permeability changes and subsequent leakage of entrapped solute. This problem can be overcome either by avoiding forming too small size liposomes of the same lipid composition as the test sampleeither before or after the packing of the column.[13, 19]

Drug Criteria for Topical Liposomal Drug Delivery System
Which groups of substances are considered to be especially interesting for liposomal encapsulation in the field of dermatology?

1. There are drugs which are known to have severe side-effects by the conventional way of topical administration, e.g. topical glucocorticosteroids.
2. There are substances which normally are effective by systemic application but not by topical application, e.g. interferon.
3. There are drugs which only show insufficient effects when applied topically. e.g. hamamelis distillate.[1, 20]

Main Fields for Application of Topical Liposome

According to the patent literature almost every kind of active ingredient might be suitable to be encapsulated into liposomes. However, among the great variety of candidates for liposome encapsulation, e.g. antifungals, antibiotics, disinfectants, immunsuppresive agents, there are three groups of drugs which are considered most often: Corticosteroids, retinoids and local anaesthetics.

Miscellaneous Field

In addition to corticosteroids, the transdermal delivery of the α-blocker bunazosin HCl, the non-steroidal antiinflammatory agent flufenamic acid, and the CAMP phosophodiesterase inhibitor dyphylline (for the treatment of psoriasis) via liposome have been

reported. Liposomes loaded with clindamycin hydrochloride were reported to show a better efficacy than non-liposome lotions in therapy of acne vulgaris.

Liposomes in Cosmetics

Recently, a great deal of interest in the use of liposomes in skin gels or skin creams has been generated in the field of cosmetics. Vegetable phospholipids are widely used for topical applications in cosmetics and dermatology, since they have a high content of esterified essential fatty acids, especially linoleic acid which is believed to increase the barrier function of the skin and decrease water loss within a short period of time after application. Soya phospholipids or other vegetable phospholipids, due to their surface activity and their ability to form liposomes, are also an ideal source for possible transport of linoleic acid into the skin.[3, 21]

Lautenschlager et al. discussed the potential use of liposomes derived from soya bean phospholipids in cosmetics. They predicted that liposome technology offers great opportunities for several new cosmetic products and that cosmetic developer would now have to deal very intensively with questions of raw material selection, characterization of raw and finished formulations, and clinical safety of these unique formulations. They suggested that Soya phospholipids in the form of liposomes satisfy many of this requirements.[22]

Marketed Formulation of Topical Liposome

a) Celadrin®

- Celadrin® Topical Liposome Lotion - 4 oz.
- Celadrin® is a registered trademark of Imagenetix, Inc.

Advantage of Celadrin® Topical Liposome

- Fast-acting
- Joint flexibility & support
- Topical Liposome Lotion with natural Menthol and MSM & Arnica
- Helps relieve joint discomfort

Product Details

Suggested Usage: Adults and children (2 yrs. of age and older), apply to affected area up to 4 times a day as needed. Massage into affected area until abosrbed into skin. Children under 2 yrs. of age:consul ta physician.

Functional Ingredients: Celadrin® (7.5%) (a proprietary blend of esterified fatty acid carbons), MSM (Methylsulphonylmethane), Arnica spp. Flower Tincture and Natural Menthol(1.25%)[Pharmaceutical Grade(U SP)].

Ingredients: De-ionized Water, Aloe *(Aloe barbadensis)* Leaf Juice, Celadrin®, MSM, Emulsifying Wax, Vegetable Glycerin, Cetyl Alcohol, Stearic Acid (vegetable source), Sweet Almond Oil, Caprylic/Capric Triglyceride, Arnica spp. Flower Tincture, Safflower Oil, Natural Menthol, Meadow foam Seed Oil, Phospholipids (from soy lecithin), Ceteareth-20, Vitamin E (as d-alpha tocopheryl acetate), Xanthan Gum and Cypress/Cedar Extract (as natural preservative).

Caution: For external use only. Avoid contact with eyes. Keep out of reach of children.[23]

## b) OptisomeTM - Encapsulated Tetracaine

Liposome-Encapsulated Tetracaine Anesthetic (LETA): Pre-Clinical

The next lead candidate in LIPPOMIX's product pipeline is a topical anesthetic cream comprising OPTISOMETM encapsulated tetracaine (5%). This formulation was found to have a more rapid onset and a deeper anesthesia of longer duration compared to two currently commercial available products: EMLA (Astra), and Ela-MAX (Ferndale). In parallel, a 1% tetracaine formulation is being partnered for sales and marketing under an Over the counter monograph. Lippomix is currently working on the development of a marketing agreement and FDA label approval.[24]

c) Lipo C™
Liposome-encapsulated Active Vitamin C with Vitamin E and Zinc

- Contains L-ascorbic acid - the only know form of vitamin C that the body can recognize and utilize for collagen production.
- Helps increase the feel of elasticity and resilience of the skin.
-

- Hypoallergenic, fragrance-free, paraben-free, contains no animal products, no mineral oil, no artificial colors, and no artificial or harmful preservatives.
- Smoothes into the skin easily and helps to restore a lustrous, healthy looking sheen to the skin.[25]
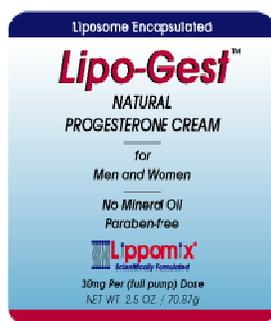
d) Lipo-Gest™
Natural Balancing Cream: A Liposome based cream

Lipo-Gest™ Natural Balancing Cream leaves the skin feeling moist, soft and natural.

Lipo-Gest™ is hypoallergenic, fragrance-free, paraben-free, contains no animal products, no mineral oil, no artificial colors, and no artificial or harmful preservatives. Lipo-Gest™ natural Balancing Cream is manufactured using Liposome™ patented technology.[26]

FUTURE PROSPECTUS

This approach is necessary because the use of liposomes for drug delivery in the future will depend on the liposome-drug formulation having clear advantages over the conventional use of the therapeutic agent not in the lcast facing comparatively higher cost of production.

Especially the liposome-cell interaction. the transport mechanisms across the stratum corneum, the role of the transfollicular pathway and the liposome-liposome interaction must be investigated in greater detail. Moreover, one must take a closer look at the behaviour of drug-loaded liposomes in healthy and diseased skin in vitro. In this context, especially skin diseases with a defect of the permeability barrier seem to be interesting. While intact liposomes are said to penetrate only the superficial parts of the living epidermis this might not hold true in diseased skin. For example, in psoriasis vulgaris, topically applied drugs encapsulated into liposomes might reach lower strata of the epidermis or even the dermis. For this reason recently reported experimental data about topical liposomal drugs (liposomal xanthines, psoralens and dithranol) in psoriasis- therapy warrant further interest.

Another promising held for therapeutical progress with topical liposome drugs is UV-induced skin cancer: Yarosh et al. investigated the effect of liposomes containing DNA repair enzymes in vitro and in vivo (animal experiments). They found that liposomes can deliver encapsulated proteins into cells of the skin leading to a reduction of UV-induced skin cancer in mice.

CONCLUSION

Generally speaking. liposomes have some advantages which make them look interesting as drug carriers for topically applied drugs. First, they are variable concerning size and surface properties and second. they can act as sustained-release depots, releasing encapsulated drugs of half-lives ranging from 0.6 to 11 days. Moreover. a new generation of liposomes, the so-called "collagen-modified liposomes" can moderate the liposome-liposome and the liposome-cell interaction due to their collagen surface properties. This indeed might mean a greater possibility to control the drug release. 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 symptomology. Such metering should also reduce the incidence of undesirable side effects arising from systemic administration, or enhanced systemic absorption of drug.

REFERENCES

1. Schmid MH and Korting HC. Therapeutic progress with topical liposome drugs for skin Disease. Advanced Drug Delivery Reviews. 1996;18:335-342.
2. Bangham AD, Standish MM and Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. Journal of Molecular Biology. 1995;13:238-252.
3. Egbaria K and Weiner N. Liposomes as a topical drug delivery system. Advanced Drug Delivery Reviews. 1990;5:287-300.
4. Gregoriadis G. The carrier potential of liposomes in biology and medicine. Journal of Medicine. 1976;295:704-710.
5. Pavelic Z, Natas S, Basnet K and Schubert R. Liposomal Gels for Vaginal Drug Delivery. Methods in Enzymology. 387:287-299.
6. Jain SK, Singh R and Sahu B. Drug Development and Industrial Pharmacy. 1997;23:827-832.
7. Schreief H and Bouwstrab J. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. Journal of Controlled Release. 1994;30:l-15.
8. Korting H, Stolz W, Schmid MH and Maierhofer G. Interaction of liposomes with human epidermis reconstructed in vitro. Journal of Dermatology. 1995;132:571-579.
9. Korting HC, Blecher P. Schafer-Korting M.,Kriftncr RW, Mezei M and Gulasekharam V. Liposomes – a selective drug delivery system for the topical route of administration: gel dosage form. Journal of Pharmaceutics and Pharmacology. 1982;34:473-474.
10. Mohammad JB. Evaluation of the Disposition and efficacy of Hydroxyzin in Liposome formulations applied topically to rabbits, The University of Manitoba Faculty of Graduate studies, January-1999.
11. Hope M and Kitson N. Liposomes a perspective for dermatologists. Journal of Dermatology and Therapeutics. 1993;11:143-154.
12. Rolland A. Particulate carriers in demal and transdermal dmg delivery: myth or reality in Pharmaceutical Particulate Carriers: Therapeutic Applications, Marcel Dekker Inc., 1993:367-421.
13. Vyas SP and Khar RK. Targeted and Controlled Drug delivery Novel carrier systems; CBS Publishers and Distributors; 2004;1:173-248.
14. Barry BW, Shroot B and Schafer H. Penetration enhancers and Skin Pharmacokinetics. 1987:121-127.
15. Korting HC, Schmid MH, Hartingcr A, Maierhofer G, Stole W and Braun F. Evidence for the phagocytosis of intact oligolamellar liposomes by human keratinocytes in vitro and consecutive intracellular desintegration. Journal of Microencapsulation. 1993;10:223-228.
16. Vyas SP and Khar RK. Formulation aspects of Liposomes. Advances in Liposomal Therapeutics. 2001;1:128-129.

17. Martin FJ and Praveen T. Pharmaceutical menufacturing of liposomes; In Specialized drug delivery Systems Manufacturing und Production Technology; Marcel Dekker. New York and Basel. 1990:267-316.
18. Batzri S and Kom ED. Single bilayer liposomes prepared without sonication. Biochint Biophysics Acta. 1973;298:1015-1019.
19. Allen TM. Removal of detergent and solvent traces from liposomes; In Liposome Technology Preparation of Liposomes. 1986;1:109- 122.
20. Korting HC, Zienicke H, Schafer-Korting M and Braun F. Liposome encapsulation improves effcacy of betamethasonc dipropionate in atopic eczema but not in psoriasis vulgaris. European Journal of Clinical Pharmacology. 1991;29:349-352.
21. Rieger MM. Skin lipids and their importance to cosmetic science. Cosmetics Toiletries. 1987;102:36-49.
22. Lautenschlager H, Roding J and Ghyczy M. The use of liposomes from soya phospholipids in cosmetics. 1988;14/88:531-534.
23. http://shopping.msn.com/prices/now-foods-celadrin-topical-liposome-lotion
24. http://www.lippomix.com/l_tetracaine.asp
25. http://www.lippomix.com/l_progesterone.asp
26. http://www.lippomix.com/p_vitaminform.asp