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Topical Liposomes: A Paradigm Shift on Topical Delivery of Drugs

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Abstract: A micro hydrodynamic focusing (MHF) technique, first suggested by Jahn et al., has successfully created monodisperse liposomes utilizing microfluidic technology. Because of their particular features, liposomes are used for medicine delivery. Indeed, they can include a wide range of hydrophilic and hydrophobic diagnostic or therapeutic agents, allowing for a greater drug payload per particle while also shielding the encapsulated compounds from metabolic processes. Many basic sciences have proven liposomes to be a promising new medication delivery method. Liposomes are tiny spheres of aqueous core and one or more lipid-based outer shells organized in a bilayer pattern. The ability to encapsulate hydrophilic and lipophilic medications and shield them from deterioration makes liposomes acceptable as better carriers. It can penetrate deeper into the skin and, as a result, provide higher absorption. It also has an affinity for the keratin of the horny layer of skin. When applied to the skin, liposomes may function as a local depot, a matrix for solubilizing poorly soluble medicines, and an enhancer of penetration while reducing their negative effects. Due to their adaptability and clinical efficacy, liposomal formulations are frequently employed in the pharmaceutical industry as drug delivery systems. They have been used to distribute medications via several routes, including oral, parenteral, and topical. Among these, topical delivery of drugs carried by liposomes exhibits interesting applications, not only for enhancing transdermal delivery of drugs intended for systemic use, thus more effectively utilizing this noninvasive alternative route to oral administration, but also for promoting dermal delivery of drugs which have to act topically, such as local anaesthetics. Topical liposome formulations have the potential to be less harmful and more effective than standard formulations. The extended and controlled release of the topical dosage forms used in liposome gel formulations may increase efficacy and patient compliance while producing therapeutically superior effects compared to standard formulations.

Keywords: Liposomes, Novel Drug Carriers, Topical Application, Therapeutic Agent, Solubilizing Agents

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1. INTRODUCTION

Liposomal formulations have been widely used over the past ten years to improve the effectiveness of medication delivered through a variety of modes of administration. Liposomal medication formulations have been demonstrated to be significantly superior to conventional dosage forms in several situations, particularly for intravenous and topical drug delivery methods. The topical application of liposomal preparations has recently garnered increased interest. At the same time, the wide list of disorders deemed candidates for systemic delivery of liposomal medications has been condensed to just a few indications[1]. In particular, for the delivery of peptides and proteins, iontophoresis and penetration enhancement are two approaches that have been investigated to boost the drug penetration rate over the skin. Here, we'll concentrate on a third potential approach: encapsulating pharmaceuticals in phospholipid-derived lipid vesicles called liposomes, which have been demonstrated to aid in drug delivery into and through skin[2]. While liposomes have been studied for a long time as parenteral drug carrier systems, particularly for the selective delivery of anticancer, antibiotic, and antifungal agents, they have only been taken into consideration for topical drug delivery, such as ophthalmic, pulmonary, and dermal/transdermal delivery for about ten years[2–5]. Liposomes, or phospholipid vesicles, are frequently used in dermatology for topically treating disorders. Liposome-encapsulated medications frequently exhibit improved skin penetration. In addition, liposomes have the potential to be applied vaginally since they can deliver a sustained and regulated release of the included substance[6,7].

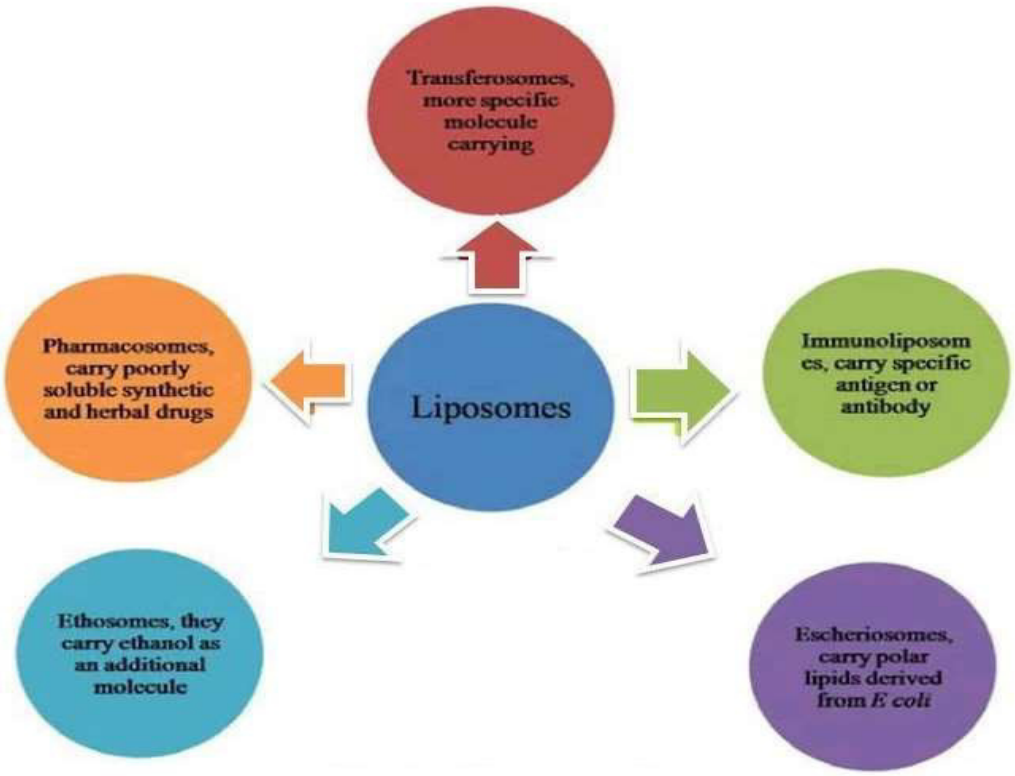

Fig 1: Represents the different kinds of Liposomes

Pharmaceuticals and cosmetics use liposomes to deliver precise and effective administration to specific skin layers. Similar to the bilayer membranes of living cells, liposomes are spherical vesicles with an aqueous core and a membrane made of amphiphilic lipids (hydrophilic lipids on one side) and lipophilic on the other) as shown in figure no. 1[8–10]. Even though liposomes showed promise for transdermal drug administration, there is a limited actual use for these formulations on the skin. However, these can be included in the gels applied to the skin. Liposomes put into gels have been proven to be stable[11]. Clinically appropriate hydrogels provide several benefits, including excellent rheological qualities, good tissue compatibility, ease of handling, and ease of application. Pharmaceutical usage of carbopol gels is permitted through several various methods of administration. These gels have good rheological qualities that result in long residual durations at the site of administration and higher and maintained skin concentrations of medications compared to ordinary gels and creams. This makes them ideal for usage topically. Delivery of medications topically is a desirable method of local and systemic therapy. Liposomes can encapsulate hydrophilic and lipophilic medications and shield them from deterioration, making them acceptable and superior carriers. It may penetrate deeper into the skin and has an affinity for the keratin in the horny layer of the skin. This allows for improved absorption. Because liposomes provide an amphiphilic environment, so they can encapsulate both hydrophilic and lipophilic molecules in their lipid bilayer and aqueous core. With this special dual-release capacity, two different types of chemicals can be delivered to the skin after application; each has a different influence on skin permeability, which may increase the desired therapeutic benefit[11,12].

1.1 Structure And Composition Of Liposome

Liposomes (fig.2) offer the highest ability to accommodate water and lipid-soluble molecules among the several novel drug delivery methods.to serve as a delivery vehicle for liposome-encapsulated medicine, releasing the active components gradually and under regulated conditions. The majority of the lipid bilayer of a liposome is made up of phospholipids. A hydrophilic head portion typically derived from egg yolk or soybean oil is covalently joined to two hydrocarbon tails comprising the lipophilic portion [13,14]. The hydrophilic head groups in a bilayer structure aggregate when they are pointed in the direction of an aqueous environment. At the same time, they encapsulate the lipophilic hydrocarbon chains[15]. Solvation of the polar head groups and hydrophobic contacts between the lipid chain while forming such a shape gives the vesicle the lowest potential energy state[16,17]. In different liposomal formulations, natural phosphatidylcholine derived from soybean oil, egg yolk, or its semi-synthetic counterparts serves as the primary component. A glycerol moiety is joined to two acyl chains that can be saturated or unsaturated in phosphatidylcholine that is found in nature. Each molecule's hydrophobic (lipophilic) component can have 10 to 24 carbon atoms, collectively making up the lipophilic portion[18]. The hydrophilic "head" comprises charged phosphate and choline molecules. The fatty acid chains can exist in either the fluid liquid-crystalline phase or the stiff, impermeable gel phase, depending on their length and saturation level. As a result, lipids can easily collect in the gel phase during storage. The temperature at which the gel phase transforms into the liquid-crystalline phase is known as the transition temperature. To enhance the retention of hydrophilic particles, increase the fluidity of the liposomal gel phase, and stabilize the bilayer membrane in a manner analogous to that of biological membranes, modest quantities of cholesterol are frequently used in liposomal formulations[19,20].

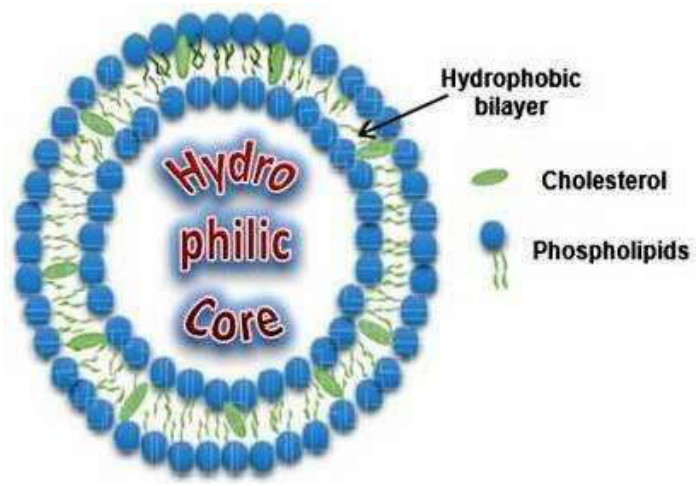

Fig.2 Shows the structure of Liposomes[20].

1.2 Advantage Of Topical Liposome

Topical medications must get to the site of action and maintain an effective concentration there for a specific period to be effective. Despite being one of the organs that can be accessed directly, applying a medicine to the skin's surface does not guarantee that it will reach the intended site of action[21]. The issue with traditional dose forms like lotions and ointments is this. When penetration enhancers like dimethylsulphoxide (DMSO) or propylene glycol are used, the transport rate across the epidermal barrier is boosted. Still, there are also greater side effects because the systemic drug level is raised. Additionally, there have been reports of irritant or even hazardous side effects, prompting experts to conclude that the inclusion of penetration enhancers does not result in better topical medication administration[22,23].

1.3 Advantages Of Liposomes As Drug Carrier Systems

1. They can easily incorporate a wide range of hydrophilic and hydrophobic pharmaceuticals because they can hold water-soluble and lipophilic compounds in their various phases, just like biological membranes can[24].
2. They have a lipid makeup similar to the epidermis, allowing them to penetrate the epidermal barrier more deeply than another dosage forms[25].
3. Studies have shown that liposomes are non-toxic and biodegradable, which is vital to prevent negative effects[26].
4. The concept of liposomes acting as "drug localizers" rather than just "drug transporters" is a pretty novel one[27].
5. Specifically, the high substantivity of liposomes with biological membranes will considerably increase medication accumulation at the site of delivery[28].
6. The regenerated epidermis takes up intact liposomes; these cysts do not penetrate healthy skin. However, in sick skin without an adequate epidermal barrier, this is to be expected[29].
7. This is crucial in medications like glucocorticoids or retinoids, known to have severe systemic side effects when absorbed more thoroughly through the skin[30].
8. Thus, systemic absorption and subsequent adverse effects would be avoided with vehicles delivering these medications to the desired action location within the skin[31].
9. Due to this, liposomes are a promising type of medication delivery for topical use.
10. 6. Liposomes can act as a local depot for the slow release of dermally active substances such as retinoic acid, corticosteroids, or antibiotics[32].
11. Individual phospholipid molecules or non-ionic ether surfactants may operate as penetration enhancers and promote cutaneous distribution, resulting in higher localized drug concentrations by penetrating the lipid layers of the stratum corneum and epidermis[33].

1.4 Mechanism Of Action Of Topical Liposome

Effective liposomal formulations require a large amount of dehydration of the solution. Since the lipid concentration in most trials is seldom reported ever reaching 100 mg/ml, the bulk aqueous medium makes up around 90% of the formulation. As a result, using liposomal systems does not offer any advantages over using a simple aqueous solution, especially if the pharmacological action is expected to start occurring a few hours after application[34]. Then, either a complete dehydration of the liposomal solution occurs, or it reaches an equilibrium state where the bilayer always retains a certain quantity of water.

The degree of a liposomal suspension's dehydration is regulated by two interrelated elements[35].

1. The phase transition temperature is the first (Tm).
2. The presence of substances that either change bilayer packing (such as cholesterol) or act as humectants or cyroprotectants, including hydrophilic polymers, glycerol, and sugars, is the second factor that frequently has an impact on Tm.

Under non-occluded conditions, the combined impact of the two variables will determine how much water the liposomal bilayer will retain after dehydration. The extent and rate of the liposomal bilayer's dehydration govern the extent and rate of drug transfer into the skin, whether the drug is hydrophobic or hydrophilic, in the absence of enhancer effects brought on by the lipid components of the liposomal bilayer's impact on skin. The following describes how hydrophobic and hydrophilic medications work after dehydration[36].

1.5 Transfer Of Hydrophobic Drugs

The lipid bilayer of the liposomes would enclose or intercalate a significant portion of the additional medication. Furthermore, maintaining the lipid bilayers above the Tm of the primary lipid is the only way to ensure optimal loading of hydrophobic medicines. As long as the lipid bilayers are in a liquid crystalline condition, the medication can move from the bilayer into the skin. The medicine will either not be transported at all or very little if the liquid crystalline phase is changed to the gel state. It has been demonstrated that dehydration of liposomal suspensions causes transitions from the liquid crystalline phase to the gel state. Therefore, the degree of dehydration will determine whether the liposomal bilayer can shift from a liquid crystalline phase to a gel state. Drug transmission from the bilayer to the skin stops if dehydration is complete and the bilayers change from their liquid crystalline state to their gel state[37]. Drug transport would be continuous and stable if dehydration reached an equilibrium stage where a certain amount of water was always retained in the bilayer—the development of a thick liposomal bilayer patch on the skin was the second effect of dryness. The development of such patches maximizes the interaction between the skin and the drug-filled bilayer and is likely treated by calcium bridges[38].

1.6 Transfer Of Hydrophilic Drugs

Liposomes transport hydrophilic drugs and their mode of action is qualitatively similar to that of hydrophobic drugs. This is sole because the water in the bilayer plays a significant role in the dehydration of the liposomal suspension. Drug transport would therefore persist for a long time in liposomal systems that maintain a consistent volume of water in the bilayer after dehydration to an equilibrium state[39]. For hydrophilic medicines, one of the main effects of dehydration is an enrichment or enhancement of drug concentration in the aqueous phase of the bilayer, which increases drug influx into and across the skin[40].

1.7 The Follicular Option

Whether or not follicles are present in the skin samples, the action outlined above still takes place. The liposomal bilayer can, however, divide and pack into the follicular or hair ducts when a follicular route is present. Since lipids are present in the follicular ducts, this partitioning is advantageous in addition to allowing unentrapped medications to be partitioned into the bilayer matrix within follicles, flooding the follicular opening with the liposomal bilayer causes entrapped drugs to be transported into the follicles[41].

1.8 Penetration Enhancer For Topical Liposome

The use of ethanol and propylene glycol enhances the skin penetration of lipophilic medicines. These solvents may facilitate medication dissolution in sebum and facilitate the opening a duct within the sebaceous glands. Despite the alcoholic solution's favourable ability to carry the medication into lipidic regions like the sebaceous glands, liposomes had the most success. Numerous studies showed that compared to non-liposomal formulations, liposomes permit a larger accumulation in the sebaceous glands. Recently, reports of drug and phospholipid dissociation in the dermis have surfaced. It suggests that whole liposomes do not enter the sebaceous glands intact[42].

1.9 Drug Criteria For Topical Liposomal Drug Delivery System

1. Some medications, such as topical glucocorticosteroids, are known to produce serious side effects when used in the traditional manner of topical administration[42].
2. Some medications, such as interferon, are typically efficacious when administered systemically but not when applied topically[43].
3. Some medications only exhibit minimal effects when given topically. such as distillate of hamamelis[44].

1.10 Main Fields For Application Of Topical Liposome

According to the patent literature, nearly every type of active substance may be acceptable for liposomal encapsulation. However, three classes of medications are most frequently taken into account out of the wide range of potential candidates for liposome encapsulation, such as antifungals, antibiotics, sanitizers, and immunosuppressive compounds corticosteroids, retinoids, and local anaesthetics[44].

1.11 Corticosteroids

When it comes to the negative effects of prolonged corticosteroid medication, such as their impact on the hypothalamic-pituitary-adrenal axis: Lower percutaneous absorption would indicate less pituitary and adrenal function depression. Furthermore, the 4-fold increase in triamcinolone content in animal skin following the application of liposomes in "lotion form" raises the prospect of lowering the

recommended dosage of corticosteroids. This also applies to liposomal "gel form" therapy, which results in a concentration five times higher in the epidermis and three times higher in the dermis. This is significant since cortisol or hydrocortisone is known to be frequently ineffective in the treatment of acute dermatoses while having no side effects when used in long-term therapy[45]. *This is why administering cortisol via liposomal delivery may be preferable to other methods.* In addition, higher medication concentrations will enhance cortisol's therapeutic effect in the epidermis and dermis14.In a clinical experiment, Korting et al. looked at how betamethasone dipropionate (BDP) in liposomal preparations (0.039% BDP) and conventional commercial preparations (0.064% BDP) affected individuals with atopic eczema or psoriasis Vulgaris. In a randomized, paired experiment, the liposomal preparation—which contained significantly less active substance—was marginally better in reducing inflammation parameters in patients with atopic eczema than the traditional BDP formulation. However, the clinical conditional improved more effectively with the traditional dosage type. This may be explained by a weakened permeability barrier, which makes it easier for liposomes to permeate the epidermis, especially in atopic eczema[46].

1.12 Retinoids

Retinoids are a promising class of drugs for liposomal encapsulation. Simple acne vulgaris is one of the key conditions for retinoid topical treatment[47]. Comedones and papules are known to be greatly reduced by commercial tretinoin gels (0.025-0.05% tretinoin) within a few weeks. However, these preparations frequently cause localized irritation and flare-up reactions when first used. The liposomal method of tretinoin administration can circumvent these traits, which frequently compromise patient compliance. According to many researchers, liposomal tretinoin treatment resulted in less irritancy in animal trials, which may be related to the drug's slow release from the liposomal formulation.[15] Comparing less concentrated liposomal medications to their commercially available conventional counterparts, they are equally effective and cause less skin irritation. A combination of enhanced bioavailability and a slower drug release may explain the similar efficacy[47].

1.13 Local Anaesthetics

Over the past few years, there have been numerous attempts to numb the skin adequately. Studies conducted a few years ago suggested that liposomal-encapsulated tetracaine and lidocaine produce superior local anaesthetic to a traditional anaesthetic cream. Due to its low drug concentration (0.5% tetracaine) and extended duration, liposomal tetracaine appears to be a strong contender[48]. Tetracaine liposomes were able to provide undamaged skin with a long-lasting anaesthetic (4 h anaesthesia after one h application under occlusion). Anaesthesia was present between 30 and 60 minutes after the liposomal preparation was applied; profound anaesthesia started between 30 and 60 minutes later. The Liposomal Tetracaine was clearly superior to the Pontocaine® cream in terms of effectiveness. Other local anaesthetics, such as lignocaine and butyl aminobenzoate, were also used with similar success for liposomal encapsulation. Tetracaine is a powerful anaesthetic that is also practical for liposomal encapsulation, making it perhaps the best choice to build an effective formulation. It can anchor in the liposome's phospholipid bilayers because of its sizable hydrophobic moiety[49,50].

1.14 Miscellaneous Drugs

In addition to corticosteroids, transdermal administration of CAMP phosphodiesterase inhibitor dyphylline (for the treatment of psoriasis) and the "-blocker bunazosin HCL via liposome have also been described. Clindamycin hydrochloride-loaded liposomes have reportedly demonstrated superior efficacy to non-liposome lotions in treating acne vulgaris[51–53]. Egbaria et al. assessed the deposition of interferon-a (IFN-a) formulated with "skin lipids" to improve the treatment of cutaneous virus infections, particularly herpes simplex virus infections, and found that liposome-associated IFN-LU was transported to deep skin layers. Similarly, over 24 hours, 70–80% of a dose of liposomal encapsulated gamma-interferon was discovered to be linked with skin. In contrast, only about one-third of the dose was deposited onto the stratum corneum. With liposomes containing the herpes simplex virus's recombinant glycoprotein D antigen, Ho et al. successfully treated herpes simplex genitalis in guinea pigs (HSV- I). This is a distinctive application of liposomes as adjuvants in a topical application that will probably be used more frequently to treat a range of localized infectious conditions[54–57]. Different Patents on topical drug delivery of Liposomes are depicted in Table No.1.

PATENTS ON TOPICAL LIPOSOMES

Name of Invention	*US Patent number*
Topical patch for liposomal drug delivery system	5, 718, 914
Liposome-based topical tretinoin formulation	Wo/1998/030215
Topical application of melatonin directly or in liposomes for the amelioration of itching and histamine and non-histamine related inflammatory skin changes	Wo/2008/036979
Liposome based topical vitamin D formulation	5, 834, 016
Ketoprofen liposome	5, 741, 515
Deoxycholic Acid liposome based dermatological topical preperation	US2006/0222695A1
Liposomal Analgesic formulation & use	6, 936, 273 B2

Table No.1 Different Patents on topical delivery of Liposomes

1.15 Regulatory Aspects Of Lipid-Based Nanocarriers

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology is the title of guidance that the USFDA published in 2014. This advice was given to the FDA's policies on items using nanotechnology. This advice states that the FDA has not explicitly defined nanotechnology, nanomaterials, or nanoscale. Instead, the advice included two things to consider when evaluating FDA-regulated products from the outset.

1) One is whether a material or final product is designed to have at least one external dimension or an internal or surface structure in the nanoscale range (approximately 1–100 nm).
2) Whether a substance or finished product is designed to have characteristics or phenomena, such as physical or chemical characteristics or biological consequences, that are due to its dimension, even if those dimensions are not nanoscale range up to 1 Mm.

2. CONCLUSION

Liposomal drug delivery is the most thoroughly researched method for treating skin conditions like psoriasis, skin cancer, and atopic dermatitis. Compared to conventional formulations, this administration strategy improves efficacy and minimizes the likelihood of side effects; it also lessens skin irritation, discolouration, and attribute-controlled release.
In addition, developing a commercial product using liposomes to treat the skin, as mentioned above, still needs to be improved by their high production costs and physical stability issues. In addition, numerous clinical investigations on skin diseases have revealed increased efficacy and better tolerance compared to standard formulations. Now, more research is required to enable the low-cost, large-scale manufacture of liposomes.

1.16 Future Prospective

We uncovered probable underlying mechanisms affecting skin penetration in the current review, which may be useful to other researchers studying the subject. We also discussed the legal and safe aspects of using such mixtures in clinical settings. This review offers the scientific community various arguments supporting the use of lipid-based nanocarriers in treating skin-related superficial fungal infections. We focused on the potential of lipid-based herbal drug delivery, how it may be utilized to increase the efficacy of herbal treatments, and the impact of nanocarriers in improving the PK-PD properties of drugs. Additionally, we have highlighted a few fresh, untried options that scientists may pursue in the future.

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4. CONFLICT OF INTEREST

Conflict of interest declared none.

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