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LIPOSOME IN COSMETIC DRUG DELIVERY SYSTEM OF PHOSPHOLIPID AND PHENOLIC COMPONENT

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ABSTRACT: Liposomes are considered to be safe for usage; they have been used hugely in cosmetics. Biologically obtained compounds of phospholipids have a high affinity to the skin's surface. Liposomes are highly permeable and have more storage capacity on the stratum corneum and also it is considered a chemically active agent to the skin. Most future studies on liposomes involve drug delivery in cosmetics. Liposome formulations are prepared from phospholipids of variant sources like egg and soya; they were differentiated in terms of their result on the skin like water content, Elasticity, Barrier function. Liposome has a variety of phospholipids giving a variety of effects on the skin humanity. Antioxidant and anti-inflammatory activity is a category poses by the plant of phenolic compound metabolite. The ideal property of the compounds are stable and also act as a bioactive ingredient in plants, but it will give the property after the process of extraction; they are considered to be very sensitive to light and heat sources; they have the property like speed metabolization, low solubility, and bioavailability. This article gives a good knowledge of liposomes in cosmetics, particularly in phospholipid and phenolic compounds additionally, it gives a view of novel methods in the formulation of liposomes and discussion about marketed liposomes in cosmetics.

INTRODUCTION: British hematologist Dr. Alec. D. Bangham and collaborators at the Babraham Institute, University of Cambridge, discovered the liposomes in 1960s [1]. Liposomes are defined as spherical vesicles that have one or more concentric bilayered phospholipid, which is enclosed in an aqueous core [2]. Topical agents application has many studies in the world of cosmetics. In Japan, the possibility of inducting cutaneous absorption was recorded, and regulatory agents became responsible for ensuring liposome products' safety and stability. The skin application treatment is based on the bilayer structure of lipid vesicles of natural membranes, it induces the ability of lipid vesicles, depending on lipids composition, to alter fluidity of cell membrane and to induce fuse with cells. It gives the delivery of active drugs to the target site [3]. The Ethanol presence in systems of lipids vesicles termed ethosomes was reported to influence the skin (Stratum Corneum) penetration and permeation of drugs to the system [4].

The obtained results should be involved in understanding the improvement of liposome penetration and the drug's skin effect. It is used in the liposomal formulation of cosmetics and dermatology applications to equilibrate the skin's moisture. Phenolic compounds encapsulation with liposome improvement in the cosmetic industry includes the characterization of phenolic compounds has extraction it's solvent-free solvent-free characteristic and null residues [5]. The bioavailability of phenolic compounds had low solubility and rapid metabolization which occur

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directly [6]; Anti-inflammatory mechanism of phenolic compounds gives the main termination to inflammation response of returning to homeostasis [7]. Application of liposomal drug delivery of cosmetic, the factors involved in the process like solubility, Shape, Size, Melting point and Purity [8].

Design of Liposome: Choose an appropriate liposome composition, functionalization, and even a targeting approach to create a good liposomal formulation, as detailed in the following sections. The choice of phospholipids, head group and chain length, and the ratio of liposome components are all important factors in determining liposome safety, stability, and efficiency [9]. Furthermore, the quantity and rigidity of lipid bilayers, size, surface charge, lipid organization, and surface modification can affect liposomes' ability to distribute drugs [10].

Property of Phospholipid Compound: Phospholipids are found in nature as biomembrane material, commonly used ingredients are soybeans (botanical base material) and egg yolk (animal-derived base material). Huge quantities of soy phospholipids are cost-efficient. A huge content of phosphatidylcholine is present in egg yolk, and it gives the property of emulsification effects. Natural Phospholipids have a group of unsaturated fatty acids, which leads to a problem in storage stability. To maintain stability in cosmetics, various situations are maintained. In an aqueous solution, they must maintain stability in oxidation and to the physical and chemical change. The physical change involved condensation, Sedimentation. The chemical change included color change, Smell change, and Lipid decomposition. Oxidation stability of Phospholipids induced by pH decrease of phospholipid dispersed solutions. Two factors for maintaining stability against oxidation are highly hydrogenation and unsaturated fatty acids with a Range of low peroxide values.

Liposomes Component and Properties: Glycerophospholipids are amphiphilic lipids made up of a glycerol molecule coupled to a phosphate group and two saturated, are the major component of liposomes (Pinot *et al.*, 2014). Phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidyl-ethanolamine (PE), phosphatidyl-inositol (PI), phosphatidylglycerol (PG), and phosphatidylserine (PS) are the types of natural phospholipids defined by this chemical group [11]. Liposomes are made up of glycerophospholipids, which are separated into two groups.

Liposome and its Structure: Liposome structures are classified according to their structure; liposomes are centrally classified on the number of lipid bilayers (lamellae) and the vesicle size. Based on their lamellarity property, liposomes can be classified as follows unilamellar (ULV -all size range), multilamellar (MLV- >500 nm), and multivesicular (MVV- >1000 nm) vesicles [12]. ULV can also be divided by their size range into three categories, small unilamellar vesicles (SUVs 20 – 100 nm), large unilamellar vesicles (LUVs - >100 nm) and giant unilamellar vesicles (GUVs - >1000 nm).

ULVs are single bilayers with more ability for the encapsulation of hydrophilic compounds. MLVs present two or more concentric lipid bilayers arranged by an onion-shaped structure, MVVs include many small non-concentric vesicles entrapped within a single lipid bilayer and are considered to be suited for the encapsulation of large volume of hydrophilic component [13]. In the vesicle size, the number of lamellae also affects the amount of compounds encapsulated in liposomes. Alternatively, a noval vesicle-type formulation is considered the multicompartment liposome (MCL).

Bioavailability of Phenolic Compounds: Phenolic compounds are stable and bioactive in plants' sources, but the extraction process is easy due to factors like pH and oxygen [14]. The bioavailability of phenolic compounds of the natural source is tempted due to its lower solubility in biological fluids and rapid metabolization in vivo. Various factors are involved in the poor bioavailability of polyphenols in harvest conditions, food processing, interaction with many compounds in the extract, and host-related factors [15]. It has issues such as low water solubility, lower stability toward light and heat during processing and storage, and its significant sensitivity to environmental factors like physical, chemical, and biological conditions are involved [16]. Many polyphenols have been formulated to solubilize and increase their bioavailability. Thermos table sensitivity is 40°C for most flavonoid compounds; for preventing degradation, variable in temperature, low solubility

and rapid metabolization affect the compound's bioavailability [17]. Pro-drug design, formulation with cyclodextrin, self-emulsifying delivery systems, gels, lipid nanocapsules, simple emulsions, nano emulsions or liposomes. Polyphenols are encapsulated by different technologies like spray drying, liposomes, inclusion, co-crystallization, nanoparticles, freeze-drying, coacervation, yeast encapsulation, and emulsions [18]. All of these formulations pay the way for improving their solubility [19]. Developing an effective drug delivery system by combining new technologies can be a good proposal to solve this drawback during formulation.

Cosmetic Applications of Phenolic Compounds against diseases:

Skin Pigmentation: Melanocytes are the reason cells for melanin synthesis related to skin pigmentation disorder. Uncontrolled melanin production could cause skin disorders like freckles, lentigines, melisma, nevus, and age spots. This synthesis is done by melanogenic enzymes like tyrosinase, tyrosinase-related protein 1, also known to be TRP-1and dopachrome tautomerase, also known as TRP-2. The study was done by phenolic enriched molecules, including phenolic and flavonoid compounds, encapsulated in liposomes to deliver drug [20].

Skin Aging Disorder: Oxidative damage (Radical species) to lipids, proteins, carbohydrates, and DNA and also 12 causing the stimulation of matrix metalloproteinases activates enzymes which cause collagen and elastin. The enzymes included are collagenase, elastase, xanthine oxidase, and tyrosinase. The peroxidation can observe epithelial inflammation in lipids caused by free radicals. The solution for this problem is phenolic extracts, one of the most effective anti-aging properties. The main Phenolic compounds are quercetin and gallic acid, which have anti-collagenase and anti-elastase agents that directly affect the skin. White tea is an example of high antioxidant properties and a high phenolic content, which presents collagenase inhibition and anti-elastase property preventing skin aging [21].

Sun Exposure Effects on Skin: The main characterization of phenolic compounds is their absorption of ultraviolet radiation (UV rays) due to chromophores. These properties prevent the sun radiation from penetrating the skin by avoiding the effects of free radicals and giving a sun-protective activity. A pre-treatment of skin with phenolic extracts like resveratrol and quercetin decreased the amount of free radicals, preventing DNA damage to the skin. Phenolic derivatives like stilbenes, flavonoids, and hydroxycinnamic acids have a high UV absorption with a sun protection factor (SPF) ranging from 7 to 29.

Effects of Anticancer in Skin: Polyphenols are considered preventive and anticancer effects on the skin. Silymarin is a polyphenolic flavonoid with the properties of antioxidants and effects of preventing photo carcinogenesis and skin cancer due to free radicals and reactive oxygen species scavenging as well as boosting the antioxidant level. Regarding mechanism, this compound inhibits mitogenic, and cell survival induces apoptosis and has a correct modulation of the cell-cycle regulators. These mechanisms it affects skin cancer promotion[22].

Novel Methods: The novel liposome preparation methods are being investigated mainly to facilitate industrial production and to be applied to a wide range of phospholipids and drugs [23]. There are novel methods based on the improvement of conventional methods, such as cross-flow injection (Wagner) method [24] and membrane contactor technology, which improved the ethanol injection method. The improved detergent removal method designs the cross-flow filtration method [25]. The direct hydration of lipid components following the sonication process represents an easy technique that avoids dissipative steps [26]. Furthermore, the supercritical fluid (SCF) technique has been explored in liposome production. These techniques use a supercritical fluid, such as carbon dioxide (CO_2), maintained under supercritical conditions in temperature and pressure.

The SCF technique offers many advantages, including a cheap and environmentally harmless solvent, controlling particle size, in situ sterilization, and the possibility of large-scale production [27]. The most used SCF techniques are injection and decompression, the rapid expansion of supercritical solutions (RESS), processes with supercritical CO_2 as an anti-solvent, gas anti-solvent (GAS), supercritical anti-solvent (SAS),

supercritical reverse-phase evaporation (SCRPE) and Aerosol solvent extraction systems (ASES). Recently, other techniques can also be employed to produce liposomes, such as dual asymmetric centrifugation and microfluidic [28]. All the novel methods referenced above have an extremely potential future in therapeutic and pharmacological applications. The main characteristics, (A) advantages, and (D) disadvantages of the novel methods are outlined in **Table 1**, based on literature review [29].

TABLE 1: THE MAIN CHARACTERISTICS, (A) ADVANTAGES AND (D) DISADVANTAGES

Method	Main Characteristic
Cross-flow injection	(A) Simple, Measurable, Sterile and continuous Process (D) organic solvent residue leads to stability problem
Membrane Contracto	(A) Simple, Measurable, Sterile and continuous Process (D) High cost, not suitable For hydrophilic drug
Cross-flow filtration	(A) Simple, Measurable, Sterile and continuous Process, Rapid (D) understudy method
RESS	(A) Simple, fast, Solvent Free process (D) Low yield
GAS	(A) Small & stable (D) Batch process
SAS	(A) Single step process (D) Difficult to optimize Condition
ASES	(A) One step process with Measurable (D) Heterogeneous and understudy process
SCRPE	(A) Simple and Reproducible Process, (D) High cost

Evaluation of Liposomal Phenolics Bioactivity *In-vitro*: Many *in-vitro* studies show phenolic liposomes' effects on the body. These phenolic compounds have the following approved activities antitumor (different types of tumour), antioxidant, anti-inflammatory, antimicrobial, and neuroprotective activity [31]. Factors like size of liposomes, phase transition temperature, pH, zeta potentials, bioaccessibility, low toxicity, release rate, and antioxidant capacity are involved in the efficacy of liposomes. These affect on the release rate of compounds and their antioxidant property. This shows the stability property of liposomes against oxidations at room temperature of at least 50°C, being good carriers for bioactive compounds. All of the studies have a biological effect achieved by phenolic-loaded liposomes *in-vitro*. In a study made by the Pires *et al.* (2019C), the antioxidant property was evaluated of polycaprolactone (PCL) prepared by electrospinning method and loaded liposomes incorporation of epigallocatechin-3-gallate (EGCG) to increase the wound-healing and enhance regeneration of skin tissue. Results obtained show that EGCG scavenges the toxic species generated by exposure to ultraviolet radiation and slows down the oxidation events and damage. In the study, bioaccessibility was increased at least sixfold after the chitosan encapsulation-coated liposomes loaded with cacao [32]. This was maintained during the spray drying technique after *in-vitro* digestion. High cholesterol to phospholipid ratio will 15 enhance the stability of the liposomes. The best formulation to produce liposomes is based on a 70:30 ratio of cholesterol /PC reaching the most stable formulation with controllable and reproducible liposomes [33]. Also, using phospholipids with a high transition temperature around 42-45°C will increase its stability property. Another observed effect was less toxicity. By loading the phenolic molecules with lipid-based nanocarriers, less toxicity is achieved [34]. Lipids are considered good materials to encapsulate phenolic components due to their hydrophobicity and potential industrial production in studying the active principle from the encapsulated phenolic molecules from Spirulina sp. LEB-18 showed a slower release rate in comparison to the free phenolic extract. In DMPC (dipalmitoylphosphatidylcholine) liposomes [35]. Another study by baicalein was encapsulated through liposomes and did not show any cytotoxic effects on PC12 and SHSY5 cells. A study showed that a liposomal curcumin formulation shows low toxicity to synovial fibroblasts and macrophages compared to the free curcumin component. The formulation was DMPC: 72 mg/ml; DMPG: 8

mg/ml; curcumin: 6.0 mg/ml also stated that this curcumin component shows liposomal formulation reduced inflammatory cytokine/chemokine expression in synovial fibroblasts without affecting the viability of the cell, for the treatment of inflammatory diseases [36]. Regarding its antioxidant property, in the previous study presented by liposomes, they were long-term oxidant stable as less.

TABLE 2: THE *IN-VITRO* STUDIES SUMMARIZATION

Type of study	Compound	Technique	Parameter & Instrumentation	Results
In-vitro study	Polyphenolic grape seed extract	High-pressure Homogenization	Size, Dynamic Light Scattering (DLS)	Increased size range from 40-100 nm,
	Annona muricata L. extraction from aqueous solution	Hydration of bilipid layer	pH, DLS	3.8
	EGCG	Homogenization Technique	Zeta potential, DLS	Mean potential of empty liposome 45 mV
	Cocoa hull waste phenolic extract (CHWPE)	Spray-drying	Bioaccessibility, CUPRAC assay	Increased at least 6 fold
	Spirulina sp LEB-18 Phenolic extract	Hydration of lipid bilayer	Release rate, FTIR, NMR, DSC	Slow-release rate
	Curcumin	Film technique	Antioxidant technique, DPPH assay	Inhibition of lipopolysaccharide

Evaluation of Liposomal Phenolics Bioactivity *In-vivo:* Several properties like low toxicity, higher stability, and anti-inflammatory effects, where shows several factors were involved like diameter size, fluidity of bilayer and charge, synthesized liposomes of syringic acid loaded having a diameter average size range of 40.01±0.48 nm, obtained by a light-scattering instrument methodology. Small particle size incorporates a direct influence on *in-vivo* time and distribution [38].

Size was also evaluated on liposomes with liquorice extraction which is obtained from the source of licorice L. roots. All of the vesicles had but 100 nm, with a highly negative zeta potential range of -32 ± 2 mV, ensuring a long-term stability effect, having the ability to include a high amount of the extract [39]. The appearance of liposomes still appeared uniform, loose and full. A hepatoprotective effect against CCl4-induced liver injury was recorded by biochemical assays [40].

CCl_4 could be a famous hepatotoxin that generates free radicals in almost 18 experimental studies in liver diseases. Within the study made, where some mice were injected with liposomes, no toxicity was reported after several doses. Rats were injected intravenously with 10, 25, or 100 mg/kg dose [41]. An anti-inflammatory effect was also reported on the liposomes loaded with liquorice extraction. These liposomes reduced TPA-induced neutrophil infiltration and allowed epidermal regeneration of the mouse. TPA is topically applied on mouse skin to induce inflammation, ulceration, oxidative stress, infiltration of inflammatory cells, horny layer loss, and oedema. A variety of 52% 42 also noticed a reduction in oedema.

Several *in-vivo* studies on mice showed the power of nanosystems to boost the efficacy of the extraction, improving the re-epithelization technique. Biochemical and histological studies of syringic acid-loaded liposomes showed an improvement in the activities of antioxidant enzymatic and non-enzymatic systems and, therefore, the lipid peroxidation reduction within the liver.

Rosemary extraction was also encapsulated through liposomes by extrusion technique, having antioxidant property. It decreases the xanthine oxidase-dependent lipid peroxidation by preventing the formation of the anion radicals, inhibiting the oxidation at a very 60%. The fluorescent intensity assay of the probe DPH-PA was wont to study the scavenging property of phenolic compounds against free radicals; these *in-vivo* studies are summarized in **Table 3.**

TABLE 3: THE *IN-VITRO* STUDIES SUMMARIZATION

Type of study	Compound	Technique	Parameter & Instrumentation	Results
In-vivo study	Syringic acid	Thin-film dispersion method	Size, Light-scattering instrument	40.01±0.48 nm
	Liquorice extract from Glycyrrhiza glabra L. roots	Hydration of the bilipid layer	Size, Light-scattering instrument	Mean diameter increased from 71 ±2 to 100 ±6 nm
	DOPE derivatives	Extrusion	Charge DLS	Negative charge is involved in prolonging the circulation time
	Chlorogenic acid	Film drying method	Toxicity Biochemical assays	Hepatoprotective effects against CCl4- induced liver injury
	Syringic acid	Thin-film dispersion method	Biochemical and histological studies	Improvement of the activities of antioxidant enzymatic and no enzymatic system
	Rosmary extract	Extrusion	Antioxidant activity	Suppresses the xanthine oxidase-dependent lipid peroxidation

Industrial Application: Encapsulation techniques are employed in various industries such as food and beverage, cosmetic, pharmaceutical, agricultural, chemical, biotechnology, and biomedical, among others. For instance, in the food and beverage industry, liposomes are accustomed decrease anthocyanins' nutritional and sensory losses and extending their stability during development, storage, and consumption, protecting the bioactive compounds not only from environmental conditions but also from degradation within the epithelial duct. In the pharmaceutical industry, quercetin-loaded liposomes are used because they act as a powerful oxygen radical scavenger in diseases involving oxidative stress.

These liposomes are useful not just for its nontoxic nature, biodegradability, and lack of immunogenic properties but also for helping the encapsulated drug to succeed in the organ. In the cosmetic industry, liposomes loaded with anthocyanins are mainly used for high lipid profile so as to assure the protection of its compounds and improve skin absorption [43].

From encapsulation techniques, liposomes are considered the sole nanoparticles available on the market since 2008, having an excellent commercial impact on the industry. The main objective of encapsulation is to act as a protective barrier against environmental conditions (light, heat, moisture, and oxygen, among others), reducing its reactivity, controlling the release of the encapsulation and adding a period to the merchandise. In the cosmetic industry, encapsulation has been a useful delivery system because of the nice challenge of passing through the skin and being highly impermeable. Many active ingredients have hydrophilic properties making it difficult to experience this layer or too hydrophilic to partition into the epidermis [44].

The most advantages of using liposomes in topical applications in dermatology are: (i) reducing side effects associated with incompatibilities; (ii) increasing drug accumulation at the skin thanks to epidermis composition; (iii) nontoxic and biodegradable liposomes characteristics(iv) easy ability to rescale for manufacturing; (v) ability to encapsulate either water and lipid-soluble active components; (vi) washing out could also be delayed providing water-resistant character; (vii) moisturize and restore the action of skin lipids membranes; (viii) localize drug depots within the skin improving the therapeutic index of the drug at the target site while reducing toxicity [45].

In an *in-vivo* study, quercetin and resveratrol loaded in liposomes ameliorated the tissue damage during a skin lesion of a mouse model. The amelioration of the tissue damage had a discount on oedema and leukocyte infiltration. This could treat diseases associated with inflammation and oxidative stress as precancerous cancerous skin lesions [46]. Some samples of cosmetic products using encapsulation techniques are shower and bath gels, moisturizers, hair products, sunscreens, tanning creams, makeup, perfumes, soaps,

exfoliants, toothpastes. Several samples of commercial products formulated with loaded liposomes with phenolic compounds are shown on **Table 4**. From the brand Sesderma®, two different serums have phenolic compounds such as ferulic acid, resveratrol, and quercetin encapsulated through liposomes to stop and treat facial photoaging, dehydration, wrinkles, and skin spots.

A product from another brand may be a mask with incorporated liposomes from Decorté®. This has anthocyanins from Murasaki-Kuromai (purple rice), which have a hydrating function to reset fatigued skin, reversing dullness and rough texture due to skin oxidation from environmental damage. Another product that also considers anthocyanins may be a skin rejuvenate cream by Mythos® containing anthocyanins from pomegranate extract. Age Defense Eye Cream from Apivita® also considers anthocyanins from secretion encapsulated in liposomes which promote skin regeneration, smoothes wrinkles and increase skin elasticity, protecting against oxidative stress and adverse environmental factors.

All the mentioned products have different liposome sizes, as shown in Table 4, but all range from 50 to 500 nm [47].

TABLE 4: COMMERCIAL PRODUCTS FORMULATED WITH LOADED LIPOSOMES WITH PHENOL COMPOUNDS

Product/ Brand	Compound	Natural source	Liposome Size
Ferulac Liposomal Serum by Sesderma ®	Ferulic acid	Apple polyphenol extract	80-120 nm
Resveraderm Antiox Serum by Sesderma ®	Resveratrol, quercetin and EGCG	Red grape extract	80-120 nm
Moisture Liposome Mask by Decorté ®	Anthocyanins	Murasaki-Kuromai (purple rice) extract	1l00 nm
Skin rejuvenate cream by Mythos ®	Anthocyanins	Punica granatum (pomegranate) extract	50-500 nm
Holistic Age Defense Eye Cream Apivita ®	Anthocyanins	Greek royal jelly extract	70-100 nm

CONCLUSION: Liposomes have gained a drug delivery system for various drugs. The application of liposomes in drugs for creative liposomes for diagnosis and treatment in various diseases and application of the therapeutic effect.

Molecules for encapsulation of liposomes are formulated for the essential component. The liposome can contribute to the easy way of delivery of cosmetic components. Phenolic components lead to increase bioavailability, stability, and encapsulation for improving characterization.

Cosmetic products give an advantage for penetration through the stratum corneum. Liposome prepared from phospholipid shows an increase in skin water content. This gives a greater advantage to the department of a dermatologist.

Liposome formulation is implied in the moisturization of the skin. To increase skin water content, egg phospholipid is marked for topical preparation in the cosmetic drug delivery system.

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