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An Overview on Novel Drug Delivery System: Phytosome and Liposomes

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ABSTRACT
Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics. For this purpose, several drug delivery systems have been formulated and are being investigated for nasal and pulmonary delivery. These include liposomes, Pytosomes, nanoparticles, proliposomes, microspheres, gels, prodrugs, cyclodextrins, among others. A strategy of using Phyto-phospholipid complexes represents a promising approach to increase the oral bioavailability of active constituents, which is consist of ‘‘label-friendly” phospholipids and active constituents. Liposome have been shown to be beneficial for stabilizing therapeutic compounds, overcoming obstacles to cellular and tissue uptake, and improving biodistribution of compounds to target sites in vivo. This enables effective delivery of encapsulated compounds to target sites while minimizing systemic toxicity. Liposomes present as an attractive delivery system due to their flexible physicochemical and biophysical properties, which allow easy manipulation to address different delivery considerations.

Keywords : Liposomes , Phytosomes, Novel Drug delivery, Phospholipid, Nanoparticles, Microparticles.

I. INTRODUCTION

Novel Drug Delivery System is an advanced drug delivery system to improve therapeutic effect and control the release of drugs. Before we comprehend the idea of a Novel Drug Delivery System (NDDS), or before we gain some insight into what made researchers develop such a new, advanced and innovative drug delivery system i.e.NDDS, let us first understand the concept of “Drug delivery”. What is drug delivery? In simple terms, it can be understood as a method or a process of administering or delivering a pharmaceutical compound in systemic circulation to achieve its therapeutic effect in humans or in animals.[1]The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all . On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics pharma codynamics, non-specific toxicity immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development . Controlled and Novel Drug Delivery which was only a dream or at best a possibility is now a reality. During the last decade and half pharmaceutical and other scientists have carried out extensive and intensive investigations in this field of drug research.

Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins,

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liposomes, and micelles. The carriers can be made slowly degradable, stimuli reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. [2]

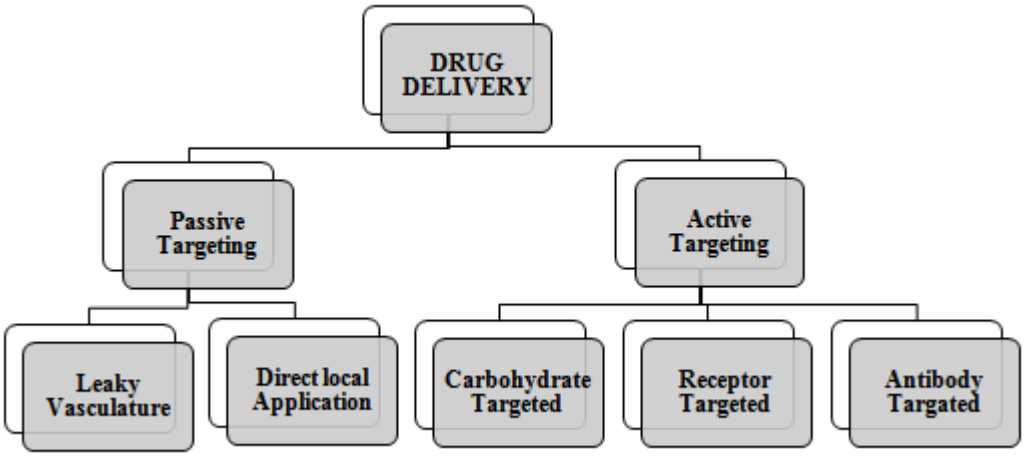

Table 1:Typesof Drug delivery system[2]

Types of novel drug delivery

1. Passive targeting
2. Active targeting[2]

Passive Targeting: Passive targeting, also known as physical targeting, is based on the preparation of a drug carrier complex that avoids removal through body mechanisms like metabolism, excretion, opsonisation, and phagocytosis.

Active targeting: Active targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic or diagnostic agent or both to a targeted diseased area within the special organ in the body.[3]

Novel drug delivery system can be divided into classes.

1. Sustained release drug delivery system
2. Controlled release drug delivery system.

Sustained release drug delivery system

It is a pharmaceutical dosage from formulated to retard the release of a therapeutic effect such that its look in the systemic circulation is delayed and/ or prolonged and the plasma profile is sustained in duration. The onset of its pharmaceutical action is often slow, and the duration of its therapeutic effect is sustained. (for example: coated granules).

Controlled release drug delivery system

This system has a meaning that goes beyond the scope of sustained drug action. It manifests a predictability and reproducibility in the drug release kinetics. The release of drug substances from a controlled release drug delivery system gains at a rate profile that is not only predictable kinetically but also reproduced from one unit to another.

They are classified as follows

I. Rate- preprogramed drug delivery system
II. Activation – Modulated drug delivery system
III. Feed – Back Regulated drug delivery system
IV. Site – Targeting drug delivery system

1. Rate- Pre-programmed drug delivery system

In this system the release of drug molecules from the drug delivery system has been pre-programmed at specific rate profiles. This was achieved by system designing which controls the molecular diffusion of drug molecule in and/or across the barrier medium in or surrounding the delivery system. e.g., Implants, Transdermal system .

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2. Activation- Modulated Drug Delivery System.

The release of drug molecule from this delivery system is activated by some physical, chemical, biochemical process and/or facilitated by the energy supplied externally. Based on the nature of the process applied or the type of energy used, these activation modulated drug delivery system can be classified.

Physical e.g., Osmotic pressure activated drug delivery system Osmotic pump.

Chemical e.g., pH activated drug delivery system

Bio Chemical e.g., Enzyme activated drug delivery system

3. Feed Back –Regulated Drug Delivery System.

The release of the drug molecule from the delivery system is activated by a triggering agent, such as biochemical substance in the body and regulated by its concentration via some feedback mechanisms. The rate of drug release is then controlled of the triggering agent detected by a sensor in the feedback regulated mechanism. e.g., Bioresponsive drug delivery system glucose triggered insulin delivery.

4. Site –Targeting drug delivery system.

In this system the drug molecules are circulating the other tissues and moving towards the specific disease site and get released. This will enhance the therapeutic effectiveness and reduces the toxicity to other healthy tissues and improve the treatment spectrum, e.g., niosomes, microspheres. [3]

Advantages of novel drug delivery system

1. Protection from physical and chemical degradation.
2. Sustained delivery.
3. Improved tissue macrophages distribution.
4. Enhancement of stability.
5. Enhancement of pharmacological activity.
6. Protection from toxicity.
7. Increased bioavailability.
8. Enhancement of solubility[4]
9. Viable treatments for previously incurable diseases
10. Potential for prophylactic applications
11. Better patient compliance. [2]

Need for Novel Drug Delivery System : An immediate release of drug takes place through conventional dosage form and hence causes oscillation of plasma drug levels. Therefore, to maintain the concentration of drug within the therapeutical window we need a novel drug delivery system in order to minimize undesired effects and maximize therapeutic benefits.

Many medications such as peptides, proteins, antibodies, vaccines, and gene-based drugs, in general, may not be taken by using conventional routes because they might be susceptible to enzymatic degradation, have poor bioavailability, poor penetration of the intestinal mucosa. Protein and peptide drugs can only be taken as injections. In order to alleviate the shortcomings, a Novel Drug Delivery System has been introduced and developed.[1]

Controlled drug release and subsequent biodegradation are important for developing successful formulations. Potential release mechanisms involve: (i) desorption of surface-bound / adsorbed drugs; (ii) diffusion through the carrier matrix; (iii) diffusion (in the case of nanocapsules) through the carrier wall; (iv) carrier matrix erosion and (v) a combined erosion / diffusion process. The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature).

For over 20 years, researchers have appreciated the potential benefits of nanotechnology in providing vast improvements in drug delivery and drug targeting. Improving delivery techniques that minimize toxicity and improve efficacy offers great potential benefits to patients andopens new markets for pharmaceutical and drug delivery companies. Other approaches to drug delivery are focused on crossing physical barriers, such as the blood–brain barrier, in order to better target the drug and improve its effectiveness; or on finding alternative and acceptable routes for the delivery of protein drugs other than via the gastrointestinal tract, where degradation can occur.[5]

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Recent developments in novel drug delivery system

1. Phytosome
2. Liposome
3. Nanoparticles
4. Emulsions
5. Microsphere
6. Ethosome
7. Solid lipid nanoparticle
8. Niosomes
9. Transdermal Drug Delivery System
10. Liquid Crystals
11. Hydrogels [4]
12. Resealed erythrocytes as drug carrier
13. Monoclonal antibodies[2]

PHYTOSOMES:

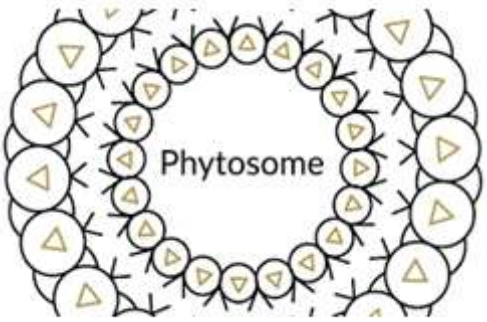

Figure1: PHYTOSOMES*[6]*

Phytosome is one of the lipid-based vesicular delivery systems which can be used for encapsulation of drugs and plant-derived nutraceuticals such as polyphenolic compounds. The Phytosome, as a newly introduced food-grade delivery system, can potentially decrease problems associated with the solubility and bioavailability of polyphenolic compounds, making them applicable in development of the new drug and food formulations. This delivery platform could benefit pharmaceutical companies regarding encapsulation of sufficient amounts of active Phytoingredients for producing new supplements. Moreover, phytosomes can enhance bioavailability of polyphenolic compounds through the gastrointestinal tract and lowering administration dosage. Furthermore, the preparation procedure of phytosomes is easy to fabricate and can be scaled up commercially. Being a potent candidate for bringing herbal-originated polyphenolic compounds into the efficient treatments of cancer and other diseases makes the Phytosome technology a great encapsulation platform to be used in the nano formulation of nutraceuticals in future.

Phytosomes are delivery systems that are structurally related to liposomes. Phytosomes are prepared through the attachment of individual ingredients of herbal extracts to phosphatidyl choline, resulting in a formulation having higher solubility and hence better absorption leading to promoted pharmacokinetic and pharmacodynamic properties compared to the conventional herbal extracts Various popular herbal extracts including ginko biloba , green tea, and ginseng have been incorporated in phytosomes. The active components of these herbal extracts were successfully bound to phosphatidyl choline.[6]

The term "Phyto" means plant, while "some" means cell- like. Over the past century, phytochemical and Phyto- pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water-soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, glycosidic aglycones etc) are poorly absorbed either due to their large molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid- rich biological membranes, resulting poor bioavailability. The Phytosome technology, developed by **Indena S.p.A.** of Italy, markedly enhances the bioavailability of select phytomedicines, by incorporating phospholipids into standardized extracts and so vastly improve their absorption and utilization .

Increased bioavailability of the phytosomes over the simpler, noncomplex plant extracts has been demonstrated by pharmacokinetic (tissue distribution) and activity studies, conducted

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in animals as well as in humans. Phytosomes has an added dimension the proven health-giving activity of the phospholipids themselves. Phytosome is also often known as Herbosomes . [7]

Advantages

1. Better stability of phytoconstituents.
2. Improve bioavailability of phytoconstituents.
3. They can also improve permeation of drug through skin.
4. It improves absorption of lipid insoluble phytoconstituents orally as well as topically.
5. Significant drug entrapment. [8]

Preparation of Phytosomes: Phytosomes can be prepared by reacting phosphatidylcholine and phytoconstituents in 1:1 ration in an aprotic solvent. In Phyto-phospholipid complex the ration between phospholipid phytoconstituent is in the range 0.5-2 mole. The most preferable ratio between phospholipid and phytoconstituents is 1:1. The phospholipid are mostly selected from group consisting of soya-lecithin phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine. Spectroscopic study shows that the molecules of phospholipid are bonded with phytoconstituents by means of chemical bonds.[8]

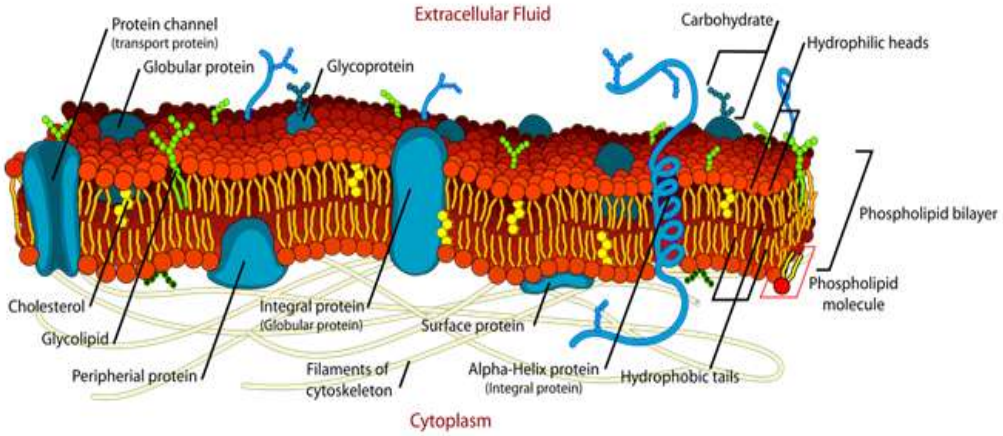

Figure 2:cell membrane largely lipid phase

Application of phytosomes in industry: The rutin Phytosome can increase the skin uptake of rutin to treat inflammation leading to pain and swelling either superficial or deep skin. Rutin phytosomes may be able to deliver rutin for a long duration as supported by the results of 24 hours permeation study, for relief in arthritis, rheumatism, athletic aches. Further investigation is needed to develop transdermal patch incorporating the optimized phytosome suitable for application on the skin surface. [9]

Table 2:Commercially available Phytosomes formulation with various therapeutic applications [10]

Product Name	Plant source	Pharmacological activity
GINSELECT PHYTOSOME®	Panax ginseng C.A. Meyer- Root	Adaptogen, tonic, Skin tightener.
LEUCOSELECT PHYTOSOME®	Vitis vinifera L. – Seed	Antioxidant, UV protectant.
VIRTIVA®	Ginkgo biloba L. – Leaf	Cognition Increaser.
VISNADEX® VISNADIN PHYTOSOME®	Ammivisnaga (L.) Lam. - Umbel without fruits	Vasokinetic

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CASPEROME™ BOSWELLIA PHYTOSOME®	Boswelliaserrata Roxb. Ex Colebr. – Resin	Anti-inflammatory, Mitigative
DIMERIC FLAVONOIDS PHYTOSOME®	Ginkgo biloba L. – Leaf	Lipolytic, Vasokinetic, PDE inhibition
CURCUMIN PHYTOSOMETM, CURCUVET®(MERIVA®)	Curcuma longa	Anti-inflammatory, osteoarthritis, anticancer
GREEN TEA PHYTOSOME™	Camellia sinensis	Nutraceutical, anticancer, Antioxidant, atherosclerosis, hepatoprotective, antidiabetic, anti-inflammatory
ECHNIACEA PHYTOSOME™	Echniacea angustifolia	Nutraceutical, immunomodulatory.
ZANTHALENE PHYTOSOME™	Zanthoxylum bungeanum	Soothing and Anti-reddening.
SERICOSIDE	Terminalia serica	Anti-aging, skin restructuring.
VITABLUE PHYTOSOME™	Vaccinium angustifolium	Antioxidant, improves vision, memory enhancer.
ESCIN ß SITOSTEROL, PHYTOSOME™	Aesculus hippocastanum	Anti-oedema and vasoactive properties
NARINGENIN PHYTOSOME™	Citrus aurantium	Antioxidant
SILYBIN PHYTOSOME™ (SILIPHOS®)	Silybium maranium	Hepatoprotective, hepatitis, cirrhosis and Inflammation.

Table 3: Recent patent on phytosomes

Patent No.	Title of Patent
EP/1844785	Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability
US 7691422	Oral compositions for the treatment of cellulite
EP1813280	Compositions comprising Ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions.
WO 2007/101551	Phospholipid complexes of curcumin having improved bioavailability
US/2007/ 0015698	Treatment of skin, and wound repair, with thymosin β4
EP1640041	Cosmetic and dermatological composition for the treatment of aging or photo damaged skin.
EP1690862	Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use.
EP2228062 A1	Compositions containing a phospholipid-curcumin complex and piperine as chemo sensitizing agent
EPO283713	Saponins with phospholipid phytosome

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WO/2004/045 541	Soluble isoflavone phytosomal compositions
EP 0464297	Complexes of neolignane derivatives with phospholipids, the use thereof and pharmaceutical and cosmetic formulations containing them.
EP 0441279	Bilobalide phospholipid complexes, their applications and formulations containing them

LIPOSOME :

A liposome is a spherical-shaped vesicle that is composed of one or more phospholipid bilayers having size range 0.5-100 um[11] which closely resembles the structure of cell membranes. The ability of liposomes to encapsulate hydrophilic or lipophilic drugs have allowed these vesicles to become useful drug delivery systems[12]

The polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilised within the phospholipid bilayer according to their affinity towards the phospholipids. Participation of non-ionic surfactants instead of phospholipids in the bilayer formation results in niosomes. Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics.Thus, drugs that are encapsulated in a nanocage functionalized with channel proteins are effectively protected from premature degradation by proteolytic enzymes. The drug molecule, however, can diffuse through between the interior and the exterior of the nanocagethe channel, driven by the concentration difference.[2]

Liposome discovery: Liposomes were discovered in the early 1960 by Bingham and co-workerssubsequently became the most extensively explored drug delivery system . Initially , though they were used to study in vitro simulated behaviour , subsequently they emerged as strong therapeutic tools most notably in drug delivery and drug targeting. [13]

Advantages of Liposomes

1) Liposomes increased efficacy and therapeutic index of drug
2) Liposome increased stability via encapsulation
3) Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations
4) Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol)
5) Liposomes help reduce the exposure of sensitive tissues to toxic drugs
6) Site avoidance effect[14]

Disadvantage of liposome

1) Low solubility
2) Short half-life
3) Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction
4) Leakage and fusion of encapsulated drug/molecules
5) Production cost is high
6) Fewer stables[14]

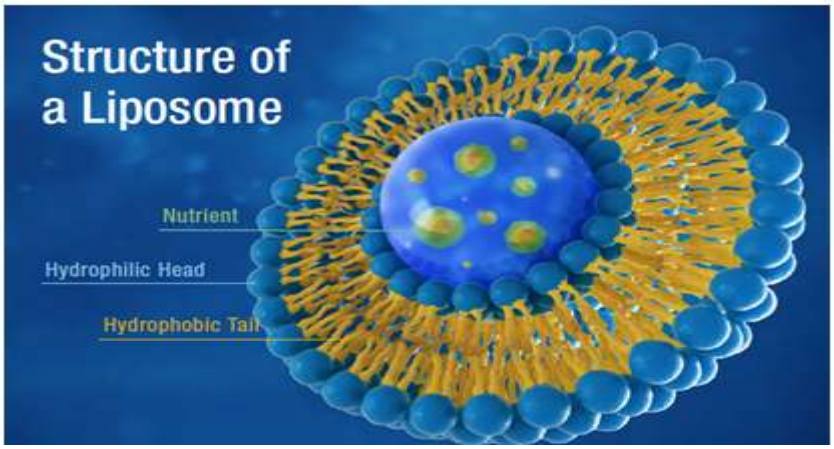

Figure 3 : Structure of liposomes

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Classification Of Liposomes

The liposome size can vary from very small (0.025 μm) to large (2.5 μm) vesicles. Moreover, liposomes may have one or bilayer membranes. The vesicle size is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes.

Based on their size and number of bilayers liposomes can also be classified into one of two categories:

(1) Multilamellar vesicles (MLV).
(2) unilamellar vesicles.

Unilamellar vesicles can also be classified into two categories:

(1) large unilamellar vesicles (LUV)
(2) small unilamellar vesicles (SUV)[15]

Multilamellar vesicles (MLV)

Production of multilamellar vesicles is the simplest method in all liposome preparations. In this method, stages of liposome generation are used as organic solvent for dissolving of lipid and drying of the resulted mixture. Combination of lipids such as egg lecithin, cholesterol and phosphatidyl glycerol in a molar ratio of 0.9:1.0:0.1 are used respectively. Chloroform or a mixture of chloroform and methanol in a typical ratio of 2:1 are used respectively. Firstly, each lipid component is dissolved in the organic solvent separately, followed by mixing in the suitable proportion with the other solubilized lipids to ensure and uniform distribution of the lipids in mixture. Afterwards, nitrogen stream is used to generate a film from the mixture in test tube. Also, in order to remove any last traces of organic solvent, the film of lipid is allowed to dry completely in an evacuated chamber for a minimum of 4-6 hours. [16]

Unilamellar vesicles preparation

The unilamellar vesicle is the most popular type of liposomes. Its liposome structure allows for an even distribution of trapped agents within a single internal aqueous compartment. There are several methods for preparation of these structures including ultrasonication, extrusion through polycarbonate filters, freeze-thawing, ethanol injection, detergent method and preparation of sterile large unilamellar vesicles. used mixture of different small unilamellar vesicles (SUVs) populations for obtain ternary GUV with uniform property. [16]

In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution. In multilamellar liposomes, vesicles have an onion structure. Classically, several unilamellar vesicles will form on the inside of the other with smaller size, making a multilamellar structure of concentric phospholipid spheres separated by layers of water. [17]

Methods of liposome preparation

General methods of preparation

All the methods of preparing the liposomes involve four basic stages:

1) Drying down lipids from organic solvent.
2) Dispersing the lipid in aqueous media.
3) Purifying the resultant liposome.
4) Analysing the final product.

Method of liposome preparation and drug loading

The following methods are used for the preparation of liposome:

1. Passive loading techniques
2. Active loading technique.

Passive loading techniques include three different methods

1. Mechanical dispersion method.
2. Solvent dispersion method.
3. Detergent removal method. (removal of non-encapsulated material)[14]

Mechanical dispersion method

The following are types of mechanical dispersion methods:

1) Sonication.
2) French pressure cell: extrusion.
3) Freeze-thawed liposomes.
4) Lipid film hydration by hand shaking non-hand. shaking or freeze drying.
5) Micro-emulsification.
6) Membrane extrusion.
7) Dried reconstituted vesicles[14]

Loading of Drugs by Liposomes

Encapsulation of Hydrophilic Drugs: Encapsulation of hydrophilic drugs results in hydration of lipids hydrophilic drugs mixture. Through such a method, drugs can enter the liposome core and other materials remain in outside part of the liposome. Remained materials will remove drug entrapment in liposome. In order to

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purify these two parts (drugs and remained outside materials), gel filtration column chromatography and dialysis are used. In addition, dehydration and rehydration method may be applied for high encapsulation of the DNA and proteins.[16]

Encapsulation of Hydrophobic Drugs: The phospholipid bilayer of liposomes is a region of hydrophobic drug encapsulation. By entrapment of this type of drugs (such as verteporfin (Visudyne)), movement of drug will be decreased towards the outer aqueous and inner parts of liposomes. These drugs are encapsulated through solubilizing of drug in the organic solvent and phospholipids. Region of drug entrapment in liposome is the hydrophobic part of liposome. Afterwards, it is possible to use laser light for activation of drug due to the treatment of wet macular degeneration.[16]

Some examples of liposomal drug with its efficacy and toxicity

Pain Management: Bupivacaine

Liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals, San Diego, CA) was approved for local surgical site injection for postoperative pain after haemorrhoidectomy and bunionectomy by the US FDA in 2011. Each liposomal bupivacaine particle (DepoFoam®, Pacira Pharmaceuticals, Parsippany, NJ) is composed of a honeycomb-like structure of internal aqueous chambers containing encapsulated bupivacaine. A single dose (266 mg) of encapsulated bupivacaine amide-based local anaesthetic is injected directly into the surgical site. A slow-release mechanism involving reorganization of the barrier lipid membranes is sustained for up to 92 h with concomitant pain control for up to 72 h, as compared to 7–12 h with standard bupivacaine. Studies show bupivacaine decreased pain compared to placebo, the use of opioids and the hospital costs. Although the liposomal bupivacaine is not a nanoparticle (3–30 μm mean diameter), it is mentioned here because it is one of the most recent liposomal formulations approved. In 2017, published the pharmacokinetic and safety profiles of LB. When administered in two doses (266 mg each) immediately, 24, 48, 72 h after the first one, the mean maximum concentration (Cmax) of bupivacaine in plasma was higher than with only one dose but did not reach the double of the Cmax from a single dose. The highest Cmax was observed in an individual taking the second dose 24 h after the first but was below toxic levels for central nervous system and cardiac. In general, LB was well tolerated and revealed no clinically relevant unsafety signs, provided excellent pain scores, lower opioids consumption, and at a lower cost. Thus, liposome formulation of the anesthetic rendered longer therapeutic times with no adverse effects.[18]

Cancer treatment: In this section, the most recent clinical studies using different liposomal drugs for the treatment of various solid cancers are described. The meaning of the endpoints in the clinical trials described here go as follows: complete response (CR): disappearance of all clinical evidences of disease or all target lesions; partial response (PR), at least 30% reduction in size of the target lesions; stable disease (SD), a 30% reduction or less than 25% increase in the size of all detectable disease; objective response rate (ORR) refers to the percentage of patients with partial or complete response to therapy (tumor reduction); “effects” refers to those effects that are attributable directly to the drug and not the natural history of the disease; progression-free survival (PFS) means the time between treatment assignments and disease progression or death, not affected by crossover or subsequent therapies and generally based on objective and quantitative assessment; events-free survival (EFS): time from treatment assignments to disease progression, death, or discontinuation of treatment for any reason (e.g., toxicity, patient preference, or initiation of a new treatment without documented progression); overall survival (OS): time from treatment assignments to patient death, irrespective of cause. Patients who are alive or missed to follow-up at the cut-off date are excluded.[18]

Liposomal Amphotericin B: During covid pandemic many patient suffer from Mucormycosis a fungal infection . so during this pandemic the drug of choice for initial therapy of mucormycosis is a lipid formulation of amphotericin B. [19] the special feature of this preparation is that it has lower nephrotoxicity and causes minimal anemia and also having less acute reaction on i.v. infusion [20]

Doxorubicin and daunorubicin: Doxil® is the first drug delivery system based on PEGylated liposome technology. It consists of encapsulated doxorubicin hydrochloride, an anticancer drug of the anthracycline family that induces caspase-dependent apoptosis in cancer cells through oxidative DNA damage by blocking topoisomerase

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IIα, an enzyme needed by cancer cells to divide and grow. This enzyme also generates free radicals (reactive oxygen species) that can lead to lipid peroxidation and membrane impairment.

The major drawback of non-liposomal or conventional anthracyclines, such as doxorubicin and daunorubicin, is their related cardiotoxicity. This is because cardiac muscle is enriched with mitochondria, which contains a high level of anionic diphosphatidylglycerol (cardiolipin) that interacts strongly with positively charged doxorubicin and can lead to lipid peroxidation within cardiac tissue. Therefore, encapsulated doxorubicin in liposomes (PLD) was developed to overcome the challenges associated with the use of free doxorubicin. In addition, PLD showed a reduced cardiac toxicity compared to non-liposomal doxorubicin.

PEGylation may extend the blood circulation time of liposomes and improve accumulation in tumor tissues, hence reducing related adverse effects (e.g., cardiotoxicity). However, PLD causes specific side effects, such as hand–foot syndrome (HFS), hypersensitivity reaction, stomatitis and mucositis. PLDs are small enough to pass through the vasculature in both tumor and healthy organs, including the skin . Thus, PLDs are secreted in sweat after intravenous infusion. This causes an oxidant/antioxidant imbalance in the skin, since doxorubicin and the Cu(II) ions that are abundant in skin tissue generate reactive oxygen species, leading to HFS lesions. As only > 3rd grade stomatitis/mucositis and HFS appeared in the PLD studies, but not in the three studies that used Myocet®, a non-PEGylated version of liposomal doxorubicin formulation (NPLD). In addition, Volgger et al. in 2015 reported no > 3rd grade stomatitis/mucositis, HFS, or cardiac toxicity in a phase II trial (n = 39) with NPLD conducted by AGO . Also, Baselga et al. reported that 9% of NPLD-treated patients showed > 3 grade stomatitis and a higher heart safety in a phase III clinical trial (n = 179) than with doxorubicin.

Other liposomal formulations with doxorubicin designed to be more tolerable and more effective than free doxorubicin have been developed, such as MM-302 and ThermoDox®. The MM-302 formulation is a HER2-targeted antibody–liposomal doxorubicin conjugate that specifically targets HER2 overexpressing cells, increasing the delivery of doxorubicin to tumor cells and limiting exposure to healthy cells, such as cardiomyocytes. the MM-302 formulation plus trastuzumab (30 mg/m^2 + 14 mg/kg IV Q3W, respectively) in a phase II trial in patients with HER2-positive locally advanced/metastatic breast cancer. ThermoDox® is a specially formulated and long-circulating lyso-thermosensitive liposomal doxorubicin that has been used clinically combined with radiofrequency ablation (RFA) to remove the core of the tumor. In a phase I trial,explored the safety and feasibility of using an extracorporeal ultrasound-guided focus ultrasound (FU), a non-invasive clinical treatment modality, to induce highly localized hyperthermia in liver tumors in order to trigger the release of doxorubicin and enhance the delivery of systemically circulating ThermoDox® (50 mg/m^2). No results have been reported in the study.[18]

Table 4: Liposomal formulation on the market

Company	Product	Status
Liposome Co., Princeton, NJ, USA	DC99: liposomal doxorubicin Ventus: liposomal PGE_1	Phase III Phase III not successful
Asta Medica, Frankfurt, Germany Aronex, The Woodlands, TX, USA	Topical anticancer cream Nyotran: liposomal nystatin Liposomal annamycin Atragen: liposomal retinoic acid	On German market Phase III Phase II Phase II
Inex, Vancouver, BC, Canada Swiss Serum Institute, Bern, Switzerland	Liposomal vincristine Epaxal: hepatitis-A vaccine Trivalent influenza vaccine Hepatitis-A and B vaccine Diphtheria, tetanus and hepatitis-A vaccines Diphtheria, tetanus, influenza and hepatitis-A vaccine	Phase I On Swiss market since 1994 Phase III Phase I Phase I Phase I

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NeXstar, Boulder, CO, USA	Spy 07: cisplatin in stealth liposomes Ambisome: amphotericin B in liposomes DaunoXome: daunorubicin in liposomes Mikasome: liposomal amikacin	Phase I On the market since 1990 (Europe) and 1997 (USA) On the market since 1996 (USA and Europe) Phase I
Novavax, Rockville, MD, USA	Escherichia Coli vaccine in synthetic liposomes Shigella flexneri vaccine	Phase I Phase I
IGI, Vineland, NJ, USA (veterinary)	Newcastle-disease vaccine (chicken) Avian-reovirus vaccine	On the market On the market
Biozone Labs, Pittsburgh, CA, USA	ELA-Max: liposomal lidocaine	On the US market since 1998
Sequus, Menlo Park, CA, USA	Doxil: doxorubicin in stealth liposomes	On the market since 1995 (USA) and 1996 (Europe)

Application of liposomes

In medicine: Applications of liposomes in pharmacology and medicine can be divided into therapeutic and diagnostic applications. Liposomes are containing drugs or various markers, and used as a model, tool, or reagent in basic studies of cell interactions, recognition processes and for mode of action of certain substances. unfortunately many drugs possess a very narrow therapeutic window, meaning that the therapeutic concentration is not much lower than the toxic one. In several cases the toxicity can be reduced, or the efficacy enhanced using an appropriate drug carrier which changes the temporal and spatial distribution of the drug. Liposomes are used to improve the solubility of lipophilic and amphiphilic drugs. Examples Porphyrins, Amphotericin B, Minoxidil, some peptides, and anthracyclines. respectively furthermore, in some cases hydrophilic drugs, such as anticancer agent doxorubicin or Acyclovir can be encapsulated in the liposome interior at concentrations several fold above their aqueous solubility. This is possible due to precipitation of the drug or e formation inside the liposome with appropriate substances encapsulated. passive targeting to the cells of the immune system, especially cells of the mononuclear phagocytic system is possible (in older literature reticuloendothelial system). Examples are Amphotericin B, porphyrins and vaccines, immunomodulators or immunosuppressor. [21]

In cosmetics: Liposomes are most widely known as spherical vesicles composed of phospholipids with an aqueous core that can be used as the delivery vehicle. For example, some studies suggested that liposomes facilitate the passage of active ingredient across the stratum corneum and transport them to the deep layers of the epidermis where they are absorbed and needed most. Liposomes is not only an effective tool to help skin absorb active cosmetic ingredients, but also improve the stability of active ingredients, increase skin hydration by surface adhesiveness, enhance dermal bioavailability and skin targeting, and protect skin cells for external stressor, such as sun or sweat. Nowadays, those properties of liposomes have been already used in cosmetic products such as moisturizers, hair shampoos, creams, lotions, etc., resulting in a revolutionary uplift of cosmetic industry.[22]

Future trends in cosmetic delivery: Through the efforts of the cosmetic industry, liposomal and nanoparticle formulations for the skin have definitively been an economic success. Molecular biology has provided us with tools to identify and build genetic materials that can be used for the treatment of hereditary diseases. The efforts made to obtain a better understanding concerning the mechanisms of the novel formulations at the molecular and supramolecular level have led to new formulation processes and could open new prospects in the area of active delivery by means of encapsulated system. Controlled release will continue to play a large part in the efficacy of cosmetics. Some trends that the consumers are

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likely to see in the future include improved systems that release their actives via pH and temperature modulation. The liposomal dispersions have proved not only to be innovative and effective cosmetic delivery systems but also very successful for preventing and treating several skin diseases. [23]

Table 4 :Commercially available cosmetic product

Name	Supplier	Application
Natipide II Liposome	Rhone-Poulenc	Reinforces skin's own moisture retention capabilities
Ultrasome	Applied Genetics	Sun-care products
Photosome	Applied Genetics	Sun-care products
Catezomes	Collaborative Labs	Versatile active delivery
Elespher	Laboratories Serobiologiques	Natural, botanical vehicle; pleasing visual effect
Microsponge	Advanced Polymer System	High payload; improves cosmetic elegance of liquid
Elesponge	Laboratories Serobiologiques	Entraps a wide range of actives whilst softening skin
LipoCD-SA	Lipo chemicals	Able to deliver oils in powder form
Unispheres	Induchem	Less sensitive to pH and surfactants; pleasing visual effect
Orgasol	Elf Atochem	Improves skin feel and adhesion, offers controlled delivery and protection to variety of hydrophilic, lipophilic substances

In agriculture: The unique value of liposomes in agricultural industry is that they can be made into model as research substitute to emulate more complex natural systems. For example, in the study of plant transport processes, liposomes serve as a model system for cellular membranes to investigate protein functionality including osmotic and pH tolerance. Liposomes can also become a model in the studies of transmembrane metabolism in plant organelles. Similarly, they can also be used in studies on pollen drying tolerance, toxin and pesticide attack on plants - liposomes are used as new carriers for slow or delayed release formulations of commercially available insecticides, which are more environmentally safe and can help the uptake of active agent into the plant's vascular system. On the other hand, biosensors based on liposome are developed to detect pesticides directly in foods and drinking water. In addition, liposomes are proven tools in veterinary to prolong the bioactivity of vaccines and anti-antibiotics.[24]

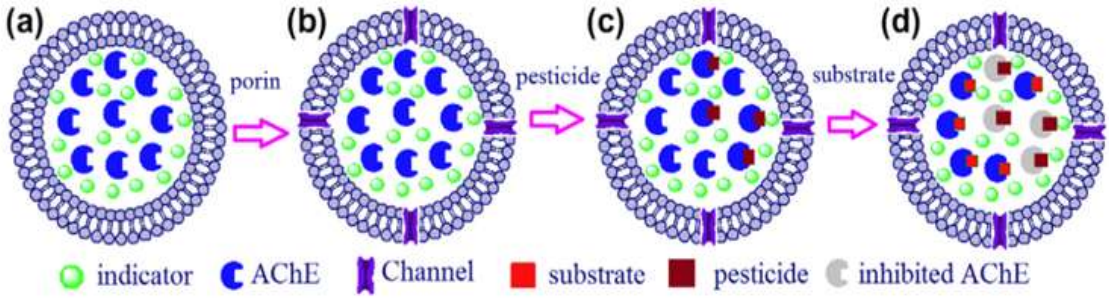

Figure4:(a) The enzyme and pyranine were encapsulated into liposomes as entrapments; (b) Membrane-embedded porins facilitate the free transport of substrate and pesticide into the liposomes; (c) After incubation of the sample, the sensitive pesticides analysis[24]

In Herbal Industry: Two companies dominate the market for these systems, namely, Cosmetochem and Indena. For herbal drug delivery, Cosmetochem launches Herbasec ® technology in markets which are actually liposomal preparations of various herbal ingredients such as extracts of White tea, Green tea, white hibiscus, Gurana, and Aloe Vera. These extracts are used in cosmetics

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because of their antioxidant effects for prevention of aging. Indena patented the technology of phytosomesand launches many products in market under this having diverse therapeutic benefits. Indena commercializes the plant constituents/ extracts of liquorice (18ß-glycyrrhetinic acid), Ammi visnaga (visnadin), Centella asiatica (triterpenes), G. biloba (ginkgo lavonglu cosides, ginkgolides, bilobalide), Hawthorn flower (vitexin-2″-O-rhamnoside), milk thistle (silymarin and Silybin), horse chestnut (escin ß-sitosterol), Terminalia sericea (sericoside), Panax ginseng (ginsenosides), grape seed (polyphenols), Green tea (polyphenols), etc.[25]

II. CONCLUSION :

Pharmaceutical development of drug delivery system is being pursued enthusiastically in many laboratories in India. These are being investigated in vitro for release pattern and in some cases in vivo in animals for pharmacokinetics but less frequently for efficacy. There is a paucity of data on clinical studies and utility of the DDS in patients. It is necessary that pharmacologists should be involved in the investigation of pharmacokinetics and pharmacodynamics of DDS if the products have reached their meaningful outcome - the clinical use.

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