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Review Article

Targeted Lipid Based Vesicles as Drug Delivery Systems in Cancer Treatment

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ABSTRACT

Cancer is not a single disease, it is a multifaced malignant tumor, having ability to develop in any part of our body and it can spread to the distant regions with the high-end cell proliferation within short duration of time. As per WHO statistics in 2023, 1 in 6 deaths occurred globally caused by cancer. Out of the available treatments to treat cancer like surgery, radiotherapy, chemotherapy, stem cell, targeted drug therapy, most promising and lifelong treatment continued by the chemotherapy agents. These drugs continuous usage may leads to the Multi Drug Resistance (MDR) and toxic effects. Application of nano therapeutical treatment with lipid vesicular systems may provide the less toxic effects, increased permeation into tumor cells, avoid the MDR effect. Lipid vesicular systems like liposomes, ethosomes and transferosomes are some of the leading drug delivery systems. Modification on the surface of the lipid layer can change the drug pharmacokinetic properties to achieve the maximum bioavailability and reduce the risk of toxicity. Plant based drugs delivery through the lipid vesicles is the majorly concerned to benefit the cancer patient with the improved nutritional support and less toxic nature of chemical compounds.

Keywords: Cancer, Chemotherapy, Lipid vesicular systems, Liposomes, MDR.

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INTRODUCTION

The term Cancer is defined by many international organizations that, Cancer is not a single disease it is a multifaced malignant tumor, which develops in any part of our body, and it can spread to the distant regions with the high-end cell proliferation within short duration of time. Abnormal and uncontrollable cell proliferation leads to damage to the organ system in our body (Brown *et al*., 2023). As per WHO statistics in 2023, 1 in 6 deaths occurred globally caused by cancer. Men are most likely to get lung, prostate, colorectal, stomach and liver cancer, whereas women are more likely to develop breast, colorectal, lung, cervical and thyroid cancer. Cancer Treatment includes surgery, chemotherapy, and radiotherapy. By modifying the lifestyle factors, we can reduce the risk analysis of the disease. New therapies like stem cell, nanoparticle, natural antioxidant, targeted drug therapy are most favorable cancer treatments to modify the disease state (Debela *et al*., 2021). Polyphenols and vitamins are the bioactive naturally occurring antioxidants to reduce the free radicals from the circulation. These natural compounds have limited usage due to less bioavailability and unstable at the gastric environment. Most often we came to know the names of plant secondary metabolites like terpenoids, alkaloids and flavonoids act as a natural remedy for cancer treatment (Chikara *et al*., 2018; Ding *et al*., 2022; Dutta, 2007).

The present study was aimed to review Nano vesicular systems to treat cancer. Vesicular systems are the carriers to encapsulate the drug particles and genetic materials to reach the target site with high efficiency. Vesicles are the concentric poly lamellar structures to load the hydrophilic, hydrophobic drug components, Nano sized particles are depicted as the Nano vesicular systems. 10^{-9} m is equal to the one Nano meter (Trucillo, 2021; Kapoor *et al*., 2023). Vesicles are made up of phospholipids or amphiphiles.

Vesicle formation mechanism includes the thermodynamic principles, molecular geometry and elastic nature of lipids. When the solute particles are dissolved in solvent, it can increase the entropy of the solution (Kapoor *et al*., 2023) Hence interaction free energy was increased. Lamellarity of vesicles depict the nature of vesicles, some of the systems have the uniflagellar and multilamellar structures. Thin layer formation depends on the nature of components and their solubility in various solvents. Self-assembly of lipids at a particular concentration is achieved by

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mixing with the aqueous layers. Incorporation of large quantities of the drug components and the enlargement of the layer size, lamellarity depends on the surface charge of the particles. Charge may play a key role in the attraction, repelling nature of the layers. Multi lamellar vesicles are ruptured by sonication to reduce the particle size. Particle shape also plays a key role in the absorption and penetration mechanism of the vesicles in to the biological barrier systems (Has and Pan, 2021; Biju *et al*., 2006).

Liposomes

Alec Bingham proposed a drug carrier system; it is almost 60 years before named as liposomes. Which are prepared by the dispersion of phospholipids in aqueous environment tends to form a concentric bilayer system ready to incorporate the drugs, diagnostic agents and DNA material. Apart from applications, there are several drawbacks related to its early clearance from the circulation and engulfed by the Reticule endothelial system of the liver. Standard storage conditions are needed to restore their properties for better effectiveness. Lipid peroxidation is the major concern related to its stability problems. 1965 is the liposomal discovered year, after this up to 2024 there are several changes got implemented to restore the therapeutically properties of the lipid compositions (Torchilin, 2005). (Figure 1 indicating the liposomal types based on structural features).

SUV-Small Uni Lamellar vesicles (around 100 nm); LUV- Large Uni Lamellar Vesicles (200 to 800 nm); GUV- Giant Uni Lamellar Vesicles; MLV- Multi Lamellar Vesicles (500 to 5000 nm). (Figure 1 represents the types of liposomes).

Liposomes are delivered its drug components into the cytoplasm based on several mechanisms like, lipid membrane ruptured at the site of contact with the cell plasma membrane to deliver its drug contents through the micro pinocytosis, adsorption of liposomes on the surface of the cell membrane to deliver the drug without any specification. The endocytosis mechanism of cell initiate by the attachment of viral components on the surface of liposomal membrane, this can allow the drug efflux into the cytoplasm. Modifications on the surface of the liposomes gives target specific nature to the liposomes, long circulation with the binding of hydrophilic polymers increase the time of spending in circulation, attachment of barium labelled liposomes on the surface to monitor their movement in body cavities as diagnostic agents, positively charged liposomes are bind to the DNA material for easy transfection mechanism (Pande, 2023; Agnusdei *et al*., 2024).

Surface of liposomes modified with attachment of proteins and peptides like Mobs, Fabs to specifically bind to the pathological target area (Table 1 represents the various types of liposomes based on specific functional category). Gene delivery also possible by polycationic nature of liposomes achieved by the acetylated polyethylene imine where cetylated end bind with surface and due to positive charge, it can anchor to DNA (Menon *et al*., 2024; Jahan *et al*., 2024).

Administration of liposomes possible in various routes, Oral route (Chitosan-insulin liposomes), aerosol liposomes were developed after drying mechanism of liposomes came into force (Aerosolized budesonide liposomes in asthma treatment in mice), Transdermal delivery of liposomes are effectively work in the skin related diseases, subcutaneous delivery of liposomes to target lymphatic systems (methotrexate to target lymphatic system), liposomes are capable of producing the humoral, cellular immune responses to the liposomal antigens (Torre *et al*., 2015).

Liposomal applications in cancer treatment

Cancer treatment has several stages with modified Therapeutical treatment with various approaches. Out of the all-cancers Prostate and breast cancer are the most commonly present cancers in men and women with respective to lung cancer (Siegel *et al*., 2023). TNM staging system is the most widely used cancer staging system to know the severity of the cancer to assess the size of Tumor (T), the involvement of regional Nodes (N) and evidence of distant Metastasis (M) (Saraswathy and Gong, 2013). Chemotherapy is the most widely used economical therapy out of all the treatments available. (Liposomes used in cancer treatment showcased in Table 2) Due to multi drug resistance system in cancer patients most of the drug combinations are dissolved in the biological cavities. MDR occurred by the drug efflux with ATP binding cassette membrane transporters (Marin *et al*., 2012; Chen *et al*., 2024; El-Tanani *et al*., 2024).

Therapeutical efficacy of the most of the chemotherapeutic agents is limited by the rapid metabolism, drug resistance and toxic side effects (Soliman, 2017; Zhang *et al*., 2025). Liposomes are the perfect solutions for the above-mentioned demerits of the chemotherapeutic agents, encapsulation of the drugs in the lipid vesicular systems give additional protection to improve solubility, enhanced drug circulation, escape from the endothelial reticulum systems, passive targeting and deposition in tumor cells, reduce the free drug concentration to limit the toxic effects (Fulton *et al*., 2023; Nsairat *et al*., 2024; Ali *et al*., 2024). (Figure 2 represents the liposomal advances in cancer therapy).

Ethosomes

Ethosomes are the lipid vesicular systems with chief constituent of Ethanol solvent to improve the flexibility of the vesicles to cross over the stratum corneum layer. The exact mechanism of using ethanol is, it can dissolve the Phospholipids of the skin layers by reducing the transition temperature of the lipids (Sguizzato *et al*., 2023). By modifying the temperature of the lipids may leads to loss its rigid nature to block the elements entering in to the skin layers, further pave the pathway to penetrate the drug components in to vasculature of dermal layers (Gupta *et al*., 2024). Basicallly ethosomes are classified into three types

based on the composition of the vesicles, like classical, binary and transethososmes (Chauhan *et al.*, 2022; Razavi *et al.*, 2015; Touitou *et al.*, 2000). (Figure 3 represents the types of ethosomes).

Ethosomes are prepared by the COLD and HOT methods. COLD method includes preparation of two solvent phases at 30°C by mixing drug, phospholipids in ethanol in solvent. HOT method includes drug, ethanol and propylene glycol phase should maintain at 40°C and add with aqueous phase which includes phospholipids (Jafari *et al.*, 2023). Ethosomes are characterized by the SEM/ TEM to know the morphology and surface characteristics (Alfehaid *et al.*, 2024). Entrapment efficiency by Ultra centrifuge which will rotate up to 20000rpm to separate the vesicles from the unentrapped drug content to know the actual drug concentration entrapped in the vesicle structures. When charge inducers are induced into the formulation, measurement of the surface charge of vesicles are performed by the Zeta potential equipment (Barupal *et al.*, 2010).

Table 1: Types of liposomes based on surface modification and its specifications.

Type of Liposomes	Specification
Long circulating liposomes	Surface of liposomes grafted with polymers.
Immune liposomes	Liposome surface attached with antibody and bind to the specific region of body parts where antigen is present.
pH sensitive liposomes	Liposome added with the pH sensitive polymers to stick to the cytoplasm of membrane in cell.

These formulations are mainly intended for the transdermal delivery of the drug products. Skin delivery of ethosomes used for the Melanoma cancer treatment to restore the mutation of melanoma cells which are essential to produce the melanin to protect skin from UV radiation (Cláudia *et al.*, 2021; Mahajan *et al.*, 2024). There are various stages of melanoma form stage I to IV as described, from initial stage to stage III, the melanoma cells enlarged to occupy the lymph nodes region from skin surface. Further cancer cell is spread to the other skin regions and organs nearby called metastasis (Shinde *et al.*, 2023).

Transferosomes

Transferosomes are first identified by civic in 1992, with property of elasticity in nano-vesicular structure (Garg *et al.*, 2016). These vesicles are smaller in size to squeeze through the skin pores by deformation of its structure and again it reforms to regain the actual structural features (Honeywell-Nguyen and Bouwstra, 2005). Skin has the 1.8 m^2 surface area to deliver the drug particles and so far, very a smaller number of drugs are delivered

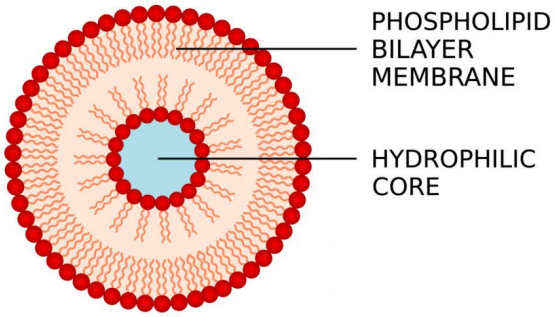

Figure 1: Types of Liposomes based on structure.

Table 2: Liposomal drug formulations with cancer application.

Liposomal formulation	Drug	Composition of liposomes	Advantage of liposomal formulation	Cancer type
Doxil	Doxorubicin	HSPC: Chol: MPEG 2000 DSPE	Reduces cardiotoxicity and Myelotoxicity	Used in Combinational therapy to treat Ovarian, breast cancer (Rommasi and Esfandiari, 2021).
Marqibo	Vincristine	Sphingomyelin: Cholesterol	Long circulation, high permeability.	Non-Hodgkin Lymphoma (Choudhury, 2020; Wang *et al.*, 2016)
Liposomal Bortizomid	Bortizomid	DSPC: MPEG 2000 DSPE: Chol (60:5:35)	Increase plasma concentration and reduce clearance.	Multiple myeloma (Zhang *et al.*, 2023).
Liposomal Paclitaxel	Paclitaxel	Egg PC: Chol: TPGS1000-TPP (88:3.5:8.5)	To treat multi drug resistance.	Lung cancer (Zhou *et al.*, 2013).
Daunorubicin	Danorubicin	DSPC: Chol (2:1)	Reduce cardiotoxicity.	Kaposi's Sarcoma (Petre and Dittmer, 2007; Olusanya *et al.*, 2018).
AmBisome	Amphotericin B	Negatively charged PC: Chol	Increase the residence time	Myeloma (Medina *et al.*, 2004; Cattel *et al.*, 2003).

d-α-tocopheryl polyethylene glycol 1000 succinate-triphenylphosphine conjugate (TPGS1000-TPP).

Table 3: Transferosomes compositions with application in the vesicular formulation.

Components of Transferosomes	Examples	Uses
Phospholipids	Soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline, Dipteral phoshatidyl choline	Vesicles forming component
Surfactant	Sod, Cholate, Sod, deoxycholate, tween-80, span-80	For providing flexibility
Alcohol	Ethanol, Methanol	As a solvent
Buffering agent	Saline phosphate buffer [pH 6.4]	As a hydrating medium
Dye	Rhodamine-123, Rhodamine-DHPE, Fluorescein-DHPE Nilered	For CSLM study

Table 4: Transferosome drug formulations with cancer application.

Drug	Composition of liposomes	Advantage of Transferosome formulation	Cancer type
Apigenin	PC, Tween80, Rhodamine.	Improve the permeation characteristics.	Melanoma cancer (Jangdey *et al.*, 2017)
5-fluorouracil	Solvent evaporation method, SPC, CHOL, SDC, Sephadex G 150.	Improve the skin permeation of drug to treat keratosis.	Non-melanoma skin cancer (Alvi *et al.*, 2011).
Methotrexate	Soya lecithin and cholesterol	Skin penetration	Non- melanoma skin cancer (Gayathri and Sangeetha, 2022).
	Soya lecithin, sodium cholate, pluronic F-68, DDTC	Skin penetration increased by the edge activator.	Non- melanoma cancer (Gupta and Trivedi, 2015).
Paclitaxel	PC, Ethanol, Chloroform, Span 80.	High controlled release of drug form transfrosomal gel formulation.	Melanoma cancer (Raahulan *et al.*, 2019)
Carvedilol	SPC, HPC, Tween 80, Sodium cholate, DSPC.	Controlled release upto 24 hr.	Melanoma and non-melanoma cancer (Chen *et al.*, 2020).
Tofacitinib citrate	Soya lecithin and cholesterol.	More percentage of drug release when compared to actual drug.	Non-melanoma cancer (Gayathri *et al.*, 2022).

by this route of administration in to the systemic circulation due to barrier function of the outermost layer of skin (Touitou, 2023). Composition of the transferosomes includes phospholipids, surface activators (surfactants) like Spans, Tweens, sodium deoxycholate, diacetyl phosphate are so far reported for the preparation (Dmello *et al.*, 2023; Firdos *et al.*, 2024). Based on the hydration gradient difference between different layers of skin, the drug delivery system transport the drug particles in to the deeper layers. Surfactants are the agents which reduce the contact within the surface regions of transferosomes and skin cells to make adaptation of that particular environment condition for easy travel into skin regions (composition of transferosomes in Table 3). Destabilizing elements and stabilizing compounds both simultaneously act to change the orientation of the particle to accommodate in the pocket size of the gap present between the corneocytes (Hua, 2015; Jain *et al.*, 2017; Cevc and Gebauer, 2003; Cevc and Blume, 1992).

Lipid vesicles are formulated by various methods like, Hand shaking method to evaporate the solvent after proper dissolution of the lipids to form multi lamellar vesicles type structure, its structure reduced by sonication (Opatha *et al.*, 2020; Firdos *et al.*, 2024). Reverse phase evaporation method to mix both the aqueous (with surfactant), organic phase (phospholipids) with sonication up to 30 min for complete miscibility of the layers where organic solvent evaporated under reduced pressure (Malakar *et al.*, 2012). Sonication method, used to vibrate the solution by ultra sonicator for a particular period of time. Ethanol injection method indicates the organic soluble lipids with surfactant solubilized in the organic solvent and inject dropwise into the aqueous solvent where the drug dissolves. The freeze thaw method is used to perform after formulation of transferosomes by exposing to the various temperatures to sudden increases and decrease.

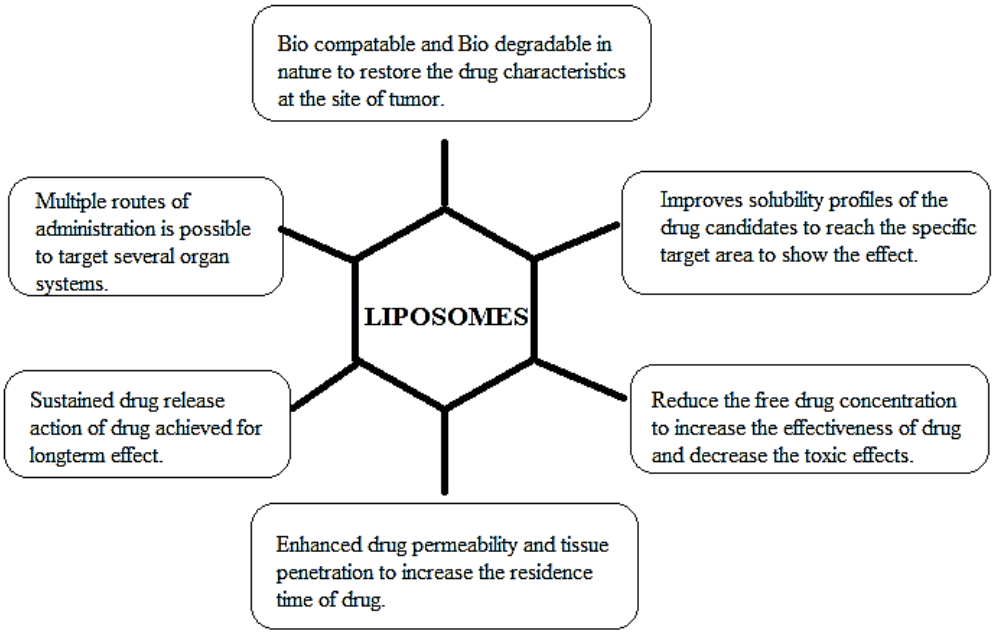

Figure 2: Liposomal advantages in cancer drug delivery systems.

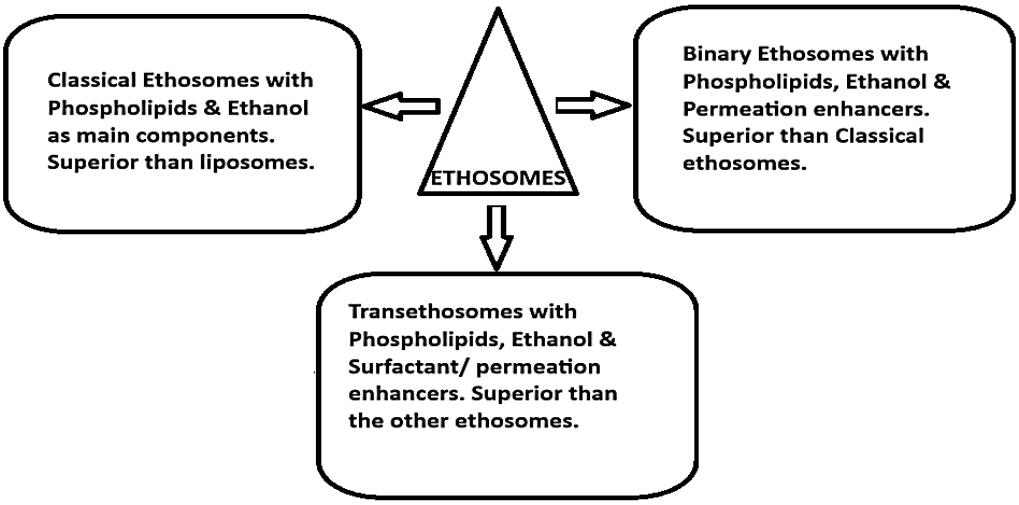

Figure 3: Classification of Ethosomes and their composition.

Transferosomes are important in the treatment of cancer (Table 4 represents the cancer applications of transferosomes), especially when it comes to applying medications topically for skin cancer. Phytoceuticals, biomacromolecules and chemotherapy can all be made more effective by penetrating the epidermal barrier with these ultra-deformable vesicles. This is particularly crucial for skin cancer since topical administration might lessen adverse effects and enhance the effectiveness of treatment.

Better Penetration

Transferosomes have the ability to penetrate epidermal barriers, allowing drugs to reach deeper levels.

Targeted Delivery

By focusing on cancer cells, they can lessen harm to healthy cells.

Combination Therapy

Photodynamic and chemotherapeutic combinations are two examples of how transferosomes can be used to deliver several medications.

Less Side Effects

Topical administration reduces systemic side effects, which makes the course of treatment more bearable.

CONCLUSION

Vesicular systems are the key particulate colloidal drug delivery systems to modify the drug release characteristics and improve the stability of the drug particles. Targeted action is more important in cancer treatment to achieve higher drug concentration with minimal side effects. Except liposomes, ethosomes and transferosomes are used to deliver the drug through the skin layers to treat melanoma/ non- melanoma skin cancer. Plant secondary metabolites having more specific activity against cancer treatment and that can be achieved by delivering these compounds in vesicular structures to overcome their drug degradation characteristics when given in oral route.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

MDR: Multi drug resistance; **WHO:** World health organization; **SUV:** Small Uni Lamellar vesicles; **LUV:** Large Uni lamellar vesicles; **GUV:** Giant Uni lamellar vesicles; **MLV:** Multi lamellar vesicles; **TNM:** Tumor node metastasis; **HSPC:** Hydrogenated soyabean phosphotidyl choline; **DSPE- PEG 2000:** 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000]; **TPGS1000-TPP:** Triphenylphosphine-Polyethyleneglycol 1000 vitamin E succinate; **PC:** Phosphotidyl choline; **CHOL:** Cholesterol; **SPC:** Soya phosphotidyl choline; **DSPC:** Distearoylphosphatidylcholine; **CSLM:** Confocal scanning laser microscopy.

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