A DISCUSSION ON THE ROLE OF COMPOSITE LIPOSOMAL TECHNOLOGIES IN THE DELIVERY OF SPECIALIZED DRUGS

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ABSTRACT

Liposomes and polymeric scaffolds may revolutionize medication delivery. Liposomes are a promising bioactive drug delivery technology, but they face several barriers to widespread medical application. Two methods can address liposomes' poor medicine delivery. The first adds functional moieties to liposome surfaces, while the second integrates depot polymeric scaffolding with pre-encapsulated drug-loaded liposomes. This seeks creative alternatives to standard liposomes' short plasma half-lives, toxicity, instability, and poor drug release control over time. This paper describes how depot polymeric scaffolds and liposome technology may alleviate the disadvantages of standard liposomes for therapeutic purposes.

INTRODUCTION

Over the past few decades, liposomes have garnered attention as a carrier system for therapeutically active compounds due to their ability to incorporate hydrophilic and hydrophobic drugs, good biocompatibility, low toxicity, lack of immune system activation, and targeted delivery of bioactive compounds to the site of action. Since liposome discovery, surface-engineered polymer conjugates functionalized with peptide, protein, and antibody and controlled size from microscale to nanoscale have been developed.

Despite extensive research into their potential as carriers for therapeutically active compounds, liposomes used in pharmaceuticals have two major drawbacks: rapid degradation by the reticuloendothelial system and inability to sustain drug delivery. These issues necessitate fresh approaches. Two polymeric techniques are presented. First, hydrophilic polymers like polyethylene glycol change liposome surfaces. Second, depot polymer-based solutions incorporate pre-encapsulated drug-loaded liposomes. Stenekes and colleagues [8] found that a transient store of polymeric components regulated the release of loaded liposomes for medical applications. This achievement offers new applications, requiring multidisciplinary research in medicine, biomaterials, chemistry, molecular biology, and cell biology. Many studies have examined temporary depot delivery devices to govern the release of pre-encapsulated drug-loaded liposomes. This technique combines polymeric- and liposome-based system advantages without their limitations. Liposome-based systems are known to be unstable, short-lived, and easily cleared. Biocompatible compared to polymer-based technologies. Polymer-based systems are more stable and supply longer than liposome-based systems.

However, poor biocompatibility, which causes drug loss during fabrication due to heat, sonication, or organic solvents, is a major problem. However, composite system increases liposome stability, regulates drug release over time, and preserves bioactivity in polymeric-based technologies. Multimodal delivery may be

more effective than polymeric- or liposome-based approaches. Thus, this study analyzes liposome-based and polymeric-based technologies and their combination for sustained drug release in temporary depot polymeric technologies. The discussion will cover depot polymeric scaffold technologies, liposome-based technologies, methods for embedding drug-loaded liposomes in a depot, and methods for managing sustained drug release rates in depot systems over time.

Liposome-Based Technology

Liposomes are microscopic aqueous vesicles closed bilayered by one or more natural phospholipids. Due to their biocompatibility and versatility, liposomes are potential drug delivery vehicles. Liposomes are predominantly egg or soybean lecithin phosphatidylcholine.

Biphasic liposomes may transport lipophilic and hydrophilic medicines. Solubility and partitioning determine drug entrapment and release in liposomes. Lipophilic drugs seldom lose molecules during storage owing to their low water solubility and near-complete entrapment in liposome lipid bilayers. Extracellular water or liposome aqueous cores may contain hydrophilic medicines. Liposomes contain hydrophilic medicines depending on bilayer composition and production.

Liposome-based medicinal innovations have been created since Bangham and colleagues identified them. Since "conventional vesicles," liposome technology has created stealth, targeted, and stimuli-sensitive liposomes. Liposome size is 50–5000 nm. Liposomes formed. Multilamellar vesicles have two or more lipid bilayers and are 500-5000 nm, whereas unilamellar ones are 50-250 nm.

Normal liposomes. Early medicinal liposomes employed traditional methods. Most liposomes include DSPC, sphingomyelin, egg phospholipids, and monosialoganglioside. Liposomal formulations only include phospholipids, which causes plasma instability and a shorter blood circulation half-life. Negative or positive liposomes are harmful, short-lived, and eliminated quickly. Lipid membrane modification initiatives have tackled similar difficulties. Cholesterol was one project. Cholesterol-based formulations delay plasma bioactive component release [28]. "Helper" lipids including cholesterol and 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) stabilized liposomes, Tran and colleagues observed. Harashima and colleagues showed liposome size caused phagocytosis. First, systemic multilamellar liposomes 500–5000 nm were suppressed. Nanoliposomes—20–50 nm unilamellar vesicles—were recently produced. Ambisone, Myocet, Daunoxome, and Daunorubicin are FDA-approved liposomals. Although tiny, unfamiliar liposomes reduce microphage absorption, poor medicine trapping remains a key drawback. Cholesterol and other phospholipids didn't fix the main issues in this investigation.

Stealth Liposomes. Stealth liposomes transport active chemicals. Immune system interception, charged liposome toxicity, low blood circulation half-life, and steric stability are all solved by this method. Hydrophilic polymer conjugates changed the liposome membrane surface for stealth liposomes.

Biocompatibility, nontoxicity, low immunogenicity, and antigenicity improved polymeric conjugates. Most hydrophilic polymer conjugates are PEG. Cross-linked lipids make liposomes hydrophilic. FDA and EU-approved stealth

liposome technology PEGylated Liposomal Doxorubicin (DOXIL/Caelyx) is great. This approach reduced macrophage absorption, increased circulation, and reduced toxicity, yet liposomes may convey active chemicals to sensitive normal and aberrant cells, limiting passive targeting. PEG-liposome diagram.

unique liposomes. Targeted liposomes were developed when stealth liposomes failed to protect sensitive normal cells or nonspecific targets from active substances in vivo. Site-specific targeting liposomes, unlike stealth liposomes, include antibodies, peptides, glycoprotein, oligopeptides, polysaccharides, growth factors, folic acid, glucose, and receptors. Drug-loaded liposome ligands are most studied peptides, proteins, and antibodies. Over expressed receptors, antigen, and selectin may increase liposomal drug accumulation in selected ligand-optimal tissues/cells. Pegylated liposomes may bind ligands by covalent, non covalent, or other coupling processes. Hydrophobic anchors, thioethers, hydrazone linkages, avidin-biotin interaction, and carboxylic acid/amine cross-linking are novel liposome ligands. Covalent coupling. Adding ligands directly to phospholipids during liposomal synthesis produces noncovalent coupling. Dual-ligand liposome conjugates targeted several cell surface receptors by Li et al. Dual-ligand increased ex vivo selectivity. Ying and colleagues generated TF-MAN dual-targeted liposomes in another study. This study employed C6 brain glioma-bearing rats in vivo and C6 cells ex vivo.

Other Types of Liposomes

Reactive liposomes and virosomes. Conventional, hidden, and targeted liposomal methods have been clinically approved. New liposomes improve endosome bioactive chemical delivery to the cytoplasm. Virosomes and stimuli-type liposomes are recent drug carriers. pH, light, magnetism, temperature, and ultrasonic vibrations stimulate. Liposomes may be virosomes. Liposome-viral envelop noncovalent union creates fusogenicity. Stimuli-sensitive liposomes release drugs, proteins, and genes based on environmental conditions. Schroeder et al., Liu and colleagues, and Lentacker and associates found that ultrasonic waves via cell membrane pore-like pores cause a liposome containing perfluorocarbon gas to transfer medicine and genes into targeted cells' cytoplasm. An external magnetic field activated liposome-loaded magnetic agents to deliver drugs to the targeted location in vivo. pH-sensitive fusogenic peptide ligands or liposomes may promote endosomal release of drug-loaded liposomes into the cytoplasm. Lyophilization may be a novel strategy to make stable liposomes, according to Chen and colleagues.

Gene-Based Liposomes. Recombinant DNA and human genome characterization have enabled gene therapies. Such technologies may treat cancer, arteriosclerosis, cystic fibrosis, haemophilia, sickle cell anemia, and genetic diseases. Protein therapy should follow gene injection. Big anionic bioactive DNA transfer is the toughest. Deoxyribonucleases degrade DNA easily.

It must also pass through the cell and nucleolar membranes without damaging the nucleus. Liposomes effectively transport DNA intracellularly. Liposomes with amine hydrophilic head groups are phospholipids. At physiological pH, cationic liposomes contain a positive surface charge from quaternary

ammonium, tertiary, secondary, or primary amines. Felgner and colleagues discovered in the late 1980s that complexing genes with liposomes increased cell absorption in vitro, leading to the use of cationic liposomes for gene delivery.

In vivo, several cationic liposomes have enhanced DNA cellular absorption and therapeutic protein synthesis by many organs. Figure 5: DNA-liposome complex schematic.

Cationic liposomes may transport DNA into live mammalian cells, but numerous challenges remain. Cationic liposome clearance slowing and customized liposome synthesis are examples. Suitable ligands may promote receptor-mediated cellular uptake. Liposomes having endosomal escape mechanisms, more effective DNA translocation to the nucleus, and rapid liposome complex dissociation before free DNA enters may be ideal.

Temporary Depot Polymeric-Based Systems for Liposomal Coupling

Polymer-based depots like hydrogel or prefabricated scaffolds release medicines, regenerative cells, proteins, growth factors, and pre-encapsulated drug-loaded liposomes over time. Many polymers have been explored for this usage because to their biodegradability, biocompatibility, nontoxicity, and inflammatory potential. Chitosan, collagen, gelatin, fibrin, alginate, dextran, carbopol, and polyvinyl alcohol are temporary depot-forming agents since they meet most of the requirements.

Injectable Polymeric Scaffolds:- Pharmaceutical and bioengineering research has sought an ideal depot for a bioactive molecule-loaded liposome with local drug retention and delayed release. In-situ-produced injectable polymer encapsulated protein and bioactive compounds as a liquid drug-loaded liposomal formulation. Injecting this fluid or suspension into the organ creates a semisolid scaffold and implant. Water, light, temperature, and pH precipitated, cross-linked, and polymerized the polymer into a semisolid and implant.

Organic or synthetic biodegradable polymers in most hydrogels released bioactive chemicals through passive diffusion, matrix pore creation, or polymeric breakdown. Phase inversion, low-glass transition temperatures, cross-linking agent hydrogels, and chemo- or thermosensitization may also affect semisolid implant formation. Subcutaneously or intratumorally, it injects drugs. Drugs stay in semisolid temporary depots. Their slow medication release and frequent injections make them inadequate medicinal carriers.

Polymer scaffolds. Prefabricated polymeric scaffolds store bioactive substances, regenerated cells, growth factors, and pre-encapsulated bioactive loaded liposomes. Unlike injectable scaffolds, solid depot polymer scaffolds are surgically implanted. Prefabricated polymeric scaffolds. Three-dimensional scaffolds contain correct surface chemistry, biodegradable or bioresorbable materials, no adverse reactions, scalable pore capacity, and reproducible shapes and sizes. Fiber bonding, emulsion freeze drying, solvent casting, high-pressure processing, gas foaming, and electrospinning satisfied requirements. This study has examined manufactured, natural, biodegradable, and nonbiodegradable polymers. Surgically removing nondegradable premade polymeric scaffolds hurts. Pre-encapsulated scaffolds release medicines constantly. Stenekes and colleagues

showed that liposomes in biodegradable depot polymeric frameworks may gently release pharmaceuticals. The inner depot's polymeric scaffold maintained the discharged liposome for days.

Natural Product-Based Liposomal Drug Delivery Systems

Collagen-liposomal medication delivery. Collagen the body's major protein is a triple helix of glycine, proline, and (hydroxy) proline [84]. collagen molecules have been found, described, and used in medicine. Biocompatibility, low antigenicity, and implantable degradability make collagen a preferred drug delivery medium. The first natural polymer for drug delivery and tissue engineering was collagen gel. Cell culture, gene therapy, and transfected fibroblast survival use biodegradable collagen scaffolds. Chemical and physical cross-linking agents were used to make collagen scaffolds. Since the 1980s, collagen and liposomes have collaborated. Drugs and other bioactive compounds were encapsulated in liposomes before being placed in a collagen-based depot with scaffolds and gels. These two approaches improved therapeutic efficacy, medication release, and storage stability.

Collagen and temperature-sensitive liposomes release calcium and phosphate ions, according to Marston et al. Collagen-based therapies and carriers are common.

Gelatin liposomes. Gelatin is made by denaturing collagen. Its biodegradability, biocompatibility, and low antigenicity make it useful in medicine. Gelatin is simple to handle because of its isoelectric point. Pharmacologists adore this trait. Tissue engineering, cell culture, and gene transfer use gelatin. Gelatin systems deliver drugs, proteins, and dual growth factors. Liposome-loaded bioactive substances may be added to PEG-gelatin gel, a porous scaffold gelatin-based temporary depot that releases drugs slowly. Gelatin-based medicine has produced issues. Poor mechanical strength and infection treatment are drawbacks.

Collagen-liposomal medicine:- Collagen the body's main protein is a triple helix of glycine, proline, and (hydroxy) proline [84]. Medicine uses 19 collagen molecules. Biocompatibility, minimal antigenicity, and implantable degradability make collagen an ideal drug delivery medium. Drug delivery and tissue engineering began with collagen gel. Cell culture, gene therapy, and transfected fibroblast survival employ biodegradable collagen scaffolds. Chemical and physical cross-linking agents created collagen scaffolds. Collagen and liposomes have worked together since 1980. Drugs and other bioactive chemicals were liposome-encapsulated and deposited in a collagen depot with scaffolds and gels. Both methods enhanced therapeutic effectiveness, drug release, and storage stability.

Marston et al. say collagen and temperature-sensitive liposomes release calcium and phosphate. Common collagen therapy and carriers. Figure 9 depicts collagen-based liposomes.

Gelatin liposomes. Denaturing collagen creates gelatin. Biodegradability, biocompatibility, and low antigenicity make it medically helpful. Isoelectric point makes gelatin easy to handle. Pharmacologists love this. Tissue engineering, cell culture, and gene transfer employ gelatin. Gelatin systems distribute medicines, proteins, and dual growth factors. PEG-gelatin gel, a porous scaffold gelatin-based temporary depot, may release liposome-loaded bioactive

compounds slowly. Gelatin-based medication has difficulties. Infection and mechanical weakness are negatives.

Pre-encapsulated liposomes and chitosan hydrogels may release cytarabine in vivo at body temperature.

Fibrin-Based Liposomal Drug Delivery. Thrombin polymerizes fibrinogen into biodegradable fibrin. Bioengineering and pharmacology have investigated fibrin-based temporary depots for decades. Biodegradability and nontoxicity of fibrin-based systems affect growth factor, gene, protein, cell, and medication transfer. Rapid polymerization formed a semirigid fibrin scaffold under physiological circumstances. Drug-loaded liposomes or chitosan matrices with bioactive agent molecules including protein, medications, and genes have been stored in fibrin-based depots. Fibrin and liposome technologies constantly released bioactive compounds.

Dextran 40 kilo-daltons are easy to get commercially. Pharmaceutics uses dextran as a medication delivery vehicle because of its unique properties. This includes biodegradability, water solubility, and biocompatibility. Dextran may deliver medicines, vaccines, and proteins, according to recent research.Drug-loaded liposomes with injectable dextran hydrogel supplied powerful anticancer agent interleukin-2. Dextran-based injectable and biodegradable drug delivery systems are made through cross-linking and photo- or free radical polymerization. In a second work, Yeo and Kohane showed that aldehyde-modified carboxymethyldextran or carboxymethylcellulose may be used to generate dextran-based hydrogels. In the same experiment, cytotoxic dextran-based devices reduced peritoneal adhesions. Macrophages and mesothelial cells showed that the crosslinked compound caused cytotoxicity. Stenekes and colleagues encapsulated a drug-loaded liposome depot in dextran polymer. The two-phase method used water, poly(ethylene glycol), and water methacylated dextran to make polymeric polymers. Liposome release was steady because dextran polymeric material degraded slowly over 100 days. The depot released entire liposomes with little size change, according to the findings. Liptay and colleagues' gene therapy trial contained chloramphenicol acetyltransferase-containing recombinant DNA in cationic liposomes and then dextran. This delivery technique lowered colon epithelial wall transfection in vivo.

Liposomal Drug Delivery Systems Based on Synthetic Polymers

Carbopol-liposomal drug delivery. Carbopol is synthetic polyacrylic acid hydrogel. Bioadhesivity, biocompatibility, and low toxicity make carbopol 980, 974NF resin, and 940 useful pharmaceutical carriers. Carbopol's functional carboxylic acid groups (-COOH) may generate hydrogen bridges to penetrate intestinal mucus and rapidly expand in water. Carbopol's carboxylic groups may hinder digestion. Salt's pH-sensitive ionic strength swelled Tang and colleagues' Carbopol-containing superporous hydrogel composites. Hosny recently shown that a hydrogel-based Carbopol depot may contain a drug-loaded liposome. In vitro research sought to increase liposome viscosity and sustained release. Medicines or loaded liposomes in carbopol depots are encapsulated and released according to vesicle charge and stiffness. The Carbopol-based system's temporary depot contains liposomal ciprofloxacin and galifloxacin. The carbopol-based system's integrated loaded

liposome administered vaginal and ophthalmic medicines successfully in these experiments.

This medication's resistance causes little damage and develops slowly. It's the best eye anti-infective. Commercial ophthalmic fluoroquinolone medicines, primarily aqueous solutions, have poor ocular bioavailability, a frequent dosing schedule, and strict patient compliance. Thus, prolonged-release ciprofloxacin liposomal hydrogel treats ocular infections well.

Modulating Drug Release from Liposomes within Polymeric Depot Systems

Prolonged release of therapeutically active compounds loaded with liposomes in a depot integrated into a polymeric-based system may minimize dosing frequency and side effects and prolong pharmacological efficacy. Machluf and colleagues demonstrated that radio-labeled protein-loaded liposomes may be embedded between two membrane layers of a polymeric-based system, such as calcium cross-linked alginate or alginate integrated with poly(l-lysine), to maintain bovine serum albumin release in vitro and in vivo. Another study suggested matrix mesh size, liposome size, diffusion, chemical, pH, and/or enzyme factors impact polymeric-based liposome release. Dhoot and Wheatley also discovered that cross-linking ions influenced barium-alginate depot liposome release. Due to their cholesterol content and manufacturing escape, liposomes spilled during encapsulation. The liposome-based system released liposomes owing to polymeric matrix breakdown, whereas the nondegradable polymer-based system released insufficiently. Nixon, Yeung, Stenekes, and others released liposomes with low and high membrane fluidity from a polymeric framework while keeping their form and size for 60 days. The liposomal burst effect dominates diffusion in pre-encapsulated drug-loaded liposomes.

The Successes and Challenges Emerging from Composite Liposome and Polymeric-Based Technologies

Polymeric-liposome systems constantly provide therapeutic chemicals in pharmaceutical applications. Liposomes in natural and manmade biodegradable polymers release genes, medications, proteins, and growth factors in various ways. Encapsulation efficiency and drug release profile affect this medicine delivery combination. Encapsulating drug-loaded liposomes effectively required cross-linking chemicals (glutaraldehyde, formaldehyde, and carbodiimide) and physical methods (UV irradiation and freeze-drying). Polymeric degradation determines the sustained release kinetics of the pre-encapsulated drug-loaded liposome. Liposome technology has benefited most from this method because polymeric materials are more stable than liposomes. By adding liposomes into a polymeric framework, continuous release, liposome stability, and pharmaceutical half-life were enhanced. Polymeric-liposome systems increase drug delivery and bioactivity. Biocompatible liposomes outperform polymers. Despite its successes, this composite system faces substantial obstacles. Proteins may lose function when harmful organic solvents or high temperatures are used in manufacturing. Most drug-loaded liposomes may stay coiled in the depot or release inadequately at the start of therapy due to polymeric component degradation. High degradation and overdose may occur together. Both depots performed worse

than degradable polymeric material due to poor drug release. Future View

Combining liposome-based technology with temporary depot polymeric technology has increased long-term drug release. Combining both medication delivery techniques has been linked to poor drug release. Designing a polymeric-based temporary depot to increase therapeutic efficacy or drug release profile is interesting because both materials are manipulable. Targeted or stimuli-sensitive liposomes may improve this system's therapy. Targeted liposome formulations may accumulate liposomal drugs in tissues and cells due to overexpressed receptors, antigens, and selectins. targets antibodies, peptides, glycoproteins, polysaccharides, growth factors, and receptors. Liposome sensitivity to pH, light, magnetism, temperature, and ultrasonic waves may improve therapy. Polymeric materials' nondegradability causes medicine release difficulties. A liposomal-based system with biodegradable, nonbiodegradable, or both polymeric components may increase depot and release. Ex vivo research should evaluate organic solvent nontoxicity. Despite system improvements, the combination technique can sustain drug-loaded liposome release from transient polymeric depots. This implantable gadget might cure chronic illnesses including Parkinson's, Alzheimer's, TB, cancer, and aids dementia complex, which need regular doses over lengthy periods of time.

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