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LIPOSOMAL TECHNOLOGY IN PHARMACEUTICAL DRUG TARGET

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ABSTRACT :- It is frequently the case in drug research that an active ingredient works well in vitro but is unable to precisely target its target in vivo. Consequently, the pharmaceutical sciences now prioritise tailored drug delivery. Liposomes have become a leading nanoparticle in targeted medication delivery since Doxil® was approved in 1995. They are used in clinical settings to treat a wide range of illnesses due to their low immunogenicity, great adaptability, and proven effectiveness. Nevertheless, each liposomal product must be developed taking into account the distinct physiological parameters that accompany each disease. Depending on the application, a wide range of targeting strategies for liposomes can be used. While active methods like conjugating targeted molecules to the liposome surface may provide even more selectivity, passive methods like PEGylation or the improved permeability and retention effect can improve overall pharmacokinetics. The purpose of this review is to provide an overview of current targeted liposome therapeutic approaches.

***Keywords*:** liposomes, drug delivery, targeted therapy, nanoparticles, active targeting, passive targeting, EPR, PEGylation.

I. INTRODUCTION :-

Significant advancements in medication delivery and discovery have been fuelled by the desire to create new treatments with better safety and efficacy profiles. But despite tremendous advancements, many promising candidates—especially in antimicrobial therapy and oncology—fail to make it from the bench to the patient's bedside. Poor solubility, low therapeutic indices, nonspecific distribution, and systemic toxicity are the main causes of this disparity[14]. These drawbacks highlight the critical need for drug delivery methods that can improve targeting, increase pharmacokinetics, and reduce side effects . Liposomes have emerged as one of the most widely explored nanocarrier systems owing to their ability to encapsulate both hydrophilic and hydrophobic drugs, protect therapeutic agents from degradation, and facilitate controlled drug release. Structurally, liposomes are spherical vesicles comprising one or more lipid bilayers surrounding an aqueous core, mimicking biological membranes [14]. Since their discovery by Alec Bangham in 1961[14], extensive research has led to significant advances in liposomal formulations, enabling improved drug bioavailability and therapeutic outcomes. Notably, sterically stabilized long-circulating liposomes (LCLs), developed through polymer coating such as PEGylation, have shown promise in prolonging systemic circulation and reducing uptake by the mononuclear phagocyte system[14]

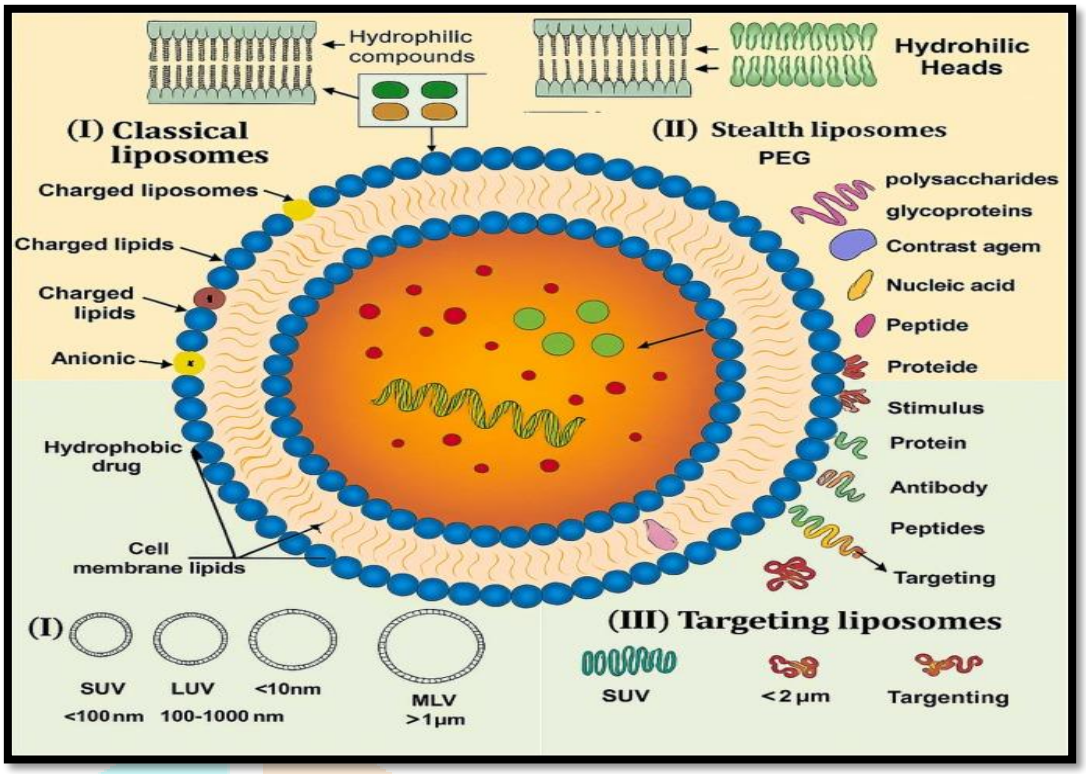

Fig. 1. Comprehensive schematic of liposome classification and structural-functional attributes for drug delivery

Three main classes are highlighted in the illustration: (i) Targeting liposomes, functionalised with ligands like peptides, antibodies, and small molecules for active targeting; (ii) Stealth liposomes, PEGylated or polysaccharide-modified to avoid immune clearance and enable prolonged circulation; and (iii) Classical liposomes, including cationic, anionic, and membrane-mimetic types, capable of encapsulating both hydrophilic and hydrophobic drugs.[14] Size and lamellarity are used to represent variations such as SUVs and MLVs. Key delivery activities such as charge modulation, ligand conjugation, and payload diversity for targeted, regulated therapeutic applications are highlighted by central and peripheral aspects. A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives [14], Liposomes: Structure, Composition, Types, and Clinical Applications [5], and Design of Liposomes as Drug Delivery Systems for Therapeutic Applications [14] are just a few of the reviews that have examined the structural diversity, drug encapsulation strategies, clinical applications, and regulatory aspects of liposomes. For example, reviews like A Comprehensive Review on Novel Liposomal Methodologies, Clinical Trials, and Patents [14] and Liposomal-Based Formulations: A Path from Basic Research to Temozolomide Delivery Inside Glioblastoma Tissue [14] focus on formulation and application strategies but offer little information on issues like immunogenicity, protein corona formation, liposomal stability, large-scale manufacturing, and storage conditions.[14]

II. FORMATION, CLASSIFICATION, AND APPLICATIONS OF LIPOSOMES IN ADVANCED DRUG DELIVERY [14]:-

Because of their adaptable structure and capabilities, liposomes are essential in a variety of biomedical domains, such as immune regulation, gene transfer, dermatology, and targeted therapy. Creating effective liposomal drug delivery systems requires a thorough understanding of their classification and uses. Liposomes can encapsulate both hydrophilic and hydrophobic medicinal substances because of their amphipathic phospholipid composition [4]. They are categorised according to preparation techniques, size, and the quantity of bilayers. Multilamellar vesicles (MLVs) are made up of several concentric bilayers, whereas unilamellar vesicles (small, big, or enormous) only have one bilayer. Conventional liposomes, stealth liposomes, cationic liposomes, and stimuli-responsive liposomes are among the functional subtypes of liposomes.[14]

A wide variety of medications are frequently encapsulated in conventional liposomes. By avoiding immune detection, polyethylene glycol (PEG)-modified stealth liposomes increase systemic circulation [5]. Because cationic liposomes interact electrostatically with negatively charged nucleic acids, they are useful for delivering genes. In order to provide controlled and site-specific medication administration, stimuli-responsive liposomes are designed to release their contents in reaction to particular environmental cues, such as pH, temperature, or enzyme activity. Liposomes are extremely versatile platforms for cutting-edge therapeutic and diagnostic applications due to their diversity in structure and function.

III. STRUCTURE AND STABILITY OF LIPOSOMES :-

Phospholipids with amphipathic characteristics, which have a hydrophilic (polar) head and a hydrophobic (nonpolar) tail, make up the majority of liposomes. The hydrophobic tail is made up of two fatty acid chains with 10–24 carbon atoms and different degrees of unsaturation, whereas the polar head usually consists of phosphoric acid connected to an alcohol [6]. The liposome's capacity to function as an efficient carrier system for both lipid-soluble and water-soluble medications is largely dependent on this molecular architecture (Fig. 2). The self-assembly characteristic of phospholipids in aquatic conditions drives the creation of bilayered liposomal structures. Phospholipids form lamellar sheets when dispersed in water and exposed to energy inputs like heating, sonication, or homogenisation. In order to reduce free energy, these sheets naturally curve, creating closed, concentric

vesicles. By balancing the interactions between lipids and water, the resultant structures achieve thermodynamic stability [8]. Liposomes are a strong platform for therapeutic delivery systems because of their bilayer structure, which stabilises the vesicles and facilitates effective drug encapsulation and regulated release. The behaviour of liposomes in biological systems is largely determined by a number of physicochemical factors, including particle size, surface charge, and PEGylation, in addition to structural and compositional characteristics. These variables have a substantial impact on circulation time, biodistribution, and interactions with biological barriers, which in turn affects how well they function in biological research and in vivo models.

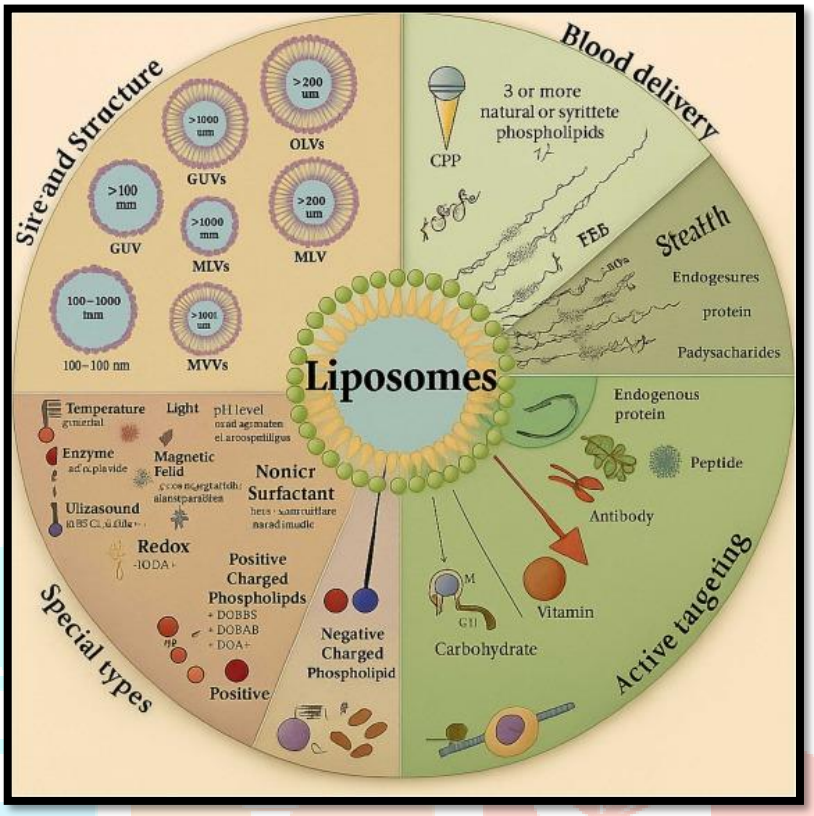

Fig. 2. Comprehensive classification of liposomes based on size, structure, composition, and functionalization[14]

IV. COMPREHENSIVE CLASSIFICATION OF LIPOSOMES: TYPES, STRUCTURES, AND FABRICATION METHODS [14]:-

Liposomes are adaptable nanocarriers that are categorised according to factors like size, bilayer count, structural alterations, and manufacturing processes. Each type of liposome is designed for a particular use in therapeutics, drug administration, and diagnostics. Multilamellar vesicles (MLVs), large unilamellar vesicles (LUVs), and small unilamellar vesicles (SUVs) are the three main types of liposomes that are often distinguished based on size and lamellarity [7], [8]. MLVs are ideal for encasing both hydrophilic and hydrophobic substances since they are made up of several concentric bilayers. LUVs are perfect for administering hydrophilic medications since they have a single bilayer and a bigger interior watery core. Increased cellular absorption and extended systemic circulation are made possible by SUVs, which likewise comprise a single bilayer but are smaller (usually <100 nm) (Table 1).

S.No	Feature	Multilamellar Vesicles (MLVs)	Large Unilamellar Vesicles (LUVs)	Small Unilamellar Vesicles (SUVs)
1	Number of Bilayers	Multiple concentric lipid bilayers	Single lipid bilayer	Single lipid bilayer
2	Size Range	500 – 5000 nm	100 – 1000 nm	< 100 nm
3	Internal Aqueous Volume	Multiple small aqueous compartments between bilayers	Large central aqueous core	Small internal volume
4	Formation Mechanism	Hydration of lipid film followed by vortexing or mechanical shaking[14]	Reverse-phase evaporation, detergent removal, or extrusion methods[14]	Sonication, ultrasonication, or high-pressure homogenization
5	Encapsulation Efficiency	High for lipophilic drugs; moderate for hydrophilic drugs[14]	High for hydrophilic drugs due to large aqueous core[14]	Low to moderate, especially for hydrophilic drugs
6	Drug Release Profile	Slow and sustained release due to multilayered barrier	Controlled release possible; faster than MLVs	Rapid release profile; useful for immediate drug availability
7	Thermodynamic Stability	High due to multiple bilayers	Moderate	Low; prone to fusion, aggregation, and leakage
8	Structural Uniformity	Heterogeneous vesicle population with broad size distribution	More homogeneous than MLVs; better suited for systemic administration	Highly uniform when properly prepared, ideal for reproducible pharmacokinetics[14]

S.No	Feature	Multilamellar Vesicles (MLVs)	Large Unilamellar Vesicles (LUVs)	Small Unilamellar Vesicles (SUVs)
9	Surface Area-to-Volume Ratio	Low	Moderate	High
10	Scalability of Preparation	Simple and easy to scale up	Moderate; requires precise equipment and process control	Difficult; requires high energy input and careful control of conditions[14]
11	Stealth Modification Potential	Less suitable	Suitable for PEGylation and surface engineering	Highly amenable to PEGylation and ligand attachment due to high surface area[14]
12	Targeting Efficiency	Limited	Can be enhanced through surface modification	High when functionalized; rapid cellular uptake
13	Typical Applications	Topical delivery, vaccine carriers, initial studies in drug loading	Delivery of hydrophilic anticancer agents, enzymes, and peptides	Systemic drug delivery, gene delivery, crossing biological barriers
14	Advantages	Simple and low-cost preparation; High lipid content; Good for lipophilic drugs[14]	Good encapsulation of hydrophilic drugs; Better control over size and structure[14]	Enhanced penetration and uptake; High circulation potential; Suitable for IV administration[14]
15	Limitations	Poor size control; Limited scalability; Lower circulation time; Difficult to sterilize[14]	Moderate stability; Limited encapsulation of hydrophobic drugs; More complex production[14]	Prone to aggregation; Lower stability; Challenging to scale up[14]

Conventional liposomes (CLs), pH-sensitive liposomes, cationic liposomes, long-circulating liposomes (LCLs), and immunoliposomes are some of the several functional forms of liposomes that have developed in terms of structural specialisation. The most basic kind of liposomes are conventional ones, which are frequently used to encapsulate common medications. In acidic settings, such tumour tissues or endosomes, pH-sensitive liposomes are made to release their payload (Fig. 2). The surface charge of cationic liposomes is positive.

Their capacity to form complexes with negatively charged nucleic acids makes them useful for delivering genes. To avoid immune clearance and achieve extended circulation, LCLs use stealth properties like polyethylene glycol (PEG). To improve therapeutic efficacy and allow for receptor-specific targeting, immunoliposomes are surface-functionalized with ligands or antibodies [7]. Reverse-phase evaporation vesicles (REVs), French press vesicles (FPVs), and ether injection vesicles (EIVs) are examples of fabrication techniques that offer clear benefits in terms of encapsulation efficiency, particle size control, and production scalability. These techniques also play a role in liposome classification. When taken as a whole, these classification schemes demonstrate how versatile liposomes are in overcoming a range of biological obstacles and maximising therapeutic delivery.

V. METHODS OF PREPARATION :-

There are various ways to formulate liposomes. The final features of liposomes are significantly influenced by the phospholipid type and the manufacturing procedure . The processes used to create liposomes can be divided into:

1.Thin film hydration method (Bangham method) :- Using a round-bottom flask, all lipids and the hydrophobic medication are dissolved in an appropriate organic solvent. A thin film layer was then produced by the organic solvent slowly evaporating under low pressure [21]. The resulting thin film is further hydrated using an aqueous buffer solution at a temperature higher than the lipid's transition temperature (Tm). A hydrophilic medication or medications to be put into the aqueous core of the liposomes may be present in the hydration solution. The effectiveness of drug encapsulation is determined by the rate of hydration, and the higher the encapsulation efficiency, the slower the rate of hydration. Both bath or probe sonicators and extrusion through polycarbonate membranes with particular pore diameters can be used to influence liposome resizing, lamellarity types, and particle distributions. Compared to sonication, the extrusion process guarantees stable liposomes with higher encapsulation efficiency. In addition to producing SUV liposomes, sonication can hydrolyse or break down medicines and/or lipids that are encapsulated. Liposome solutions may get contaminated with metals due to probe sonication (Figure 8).

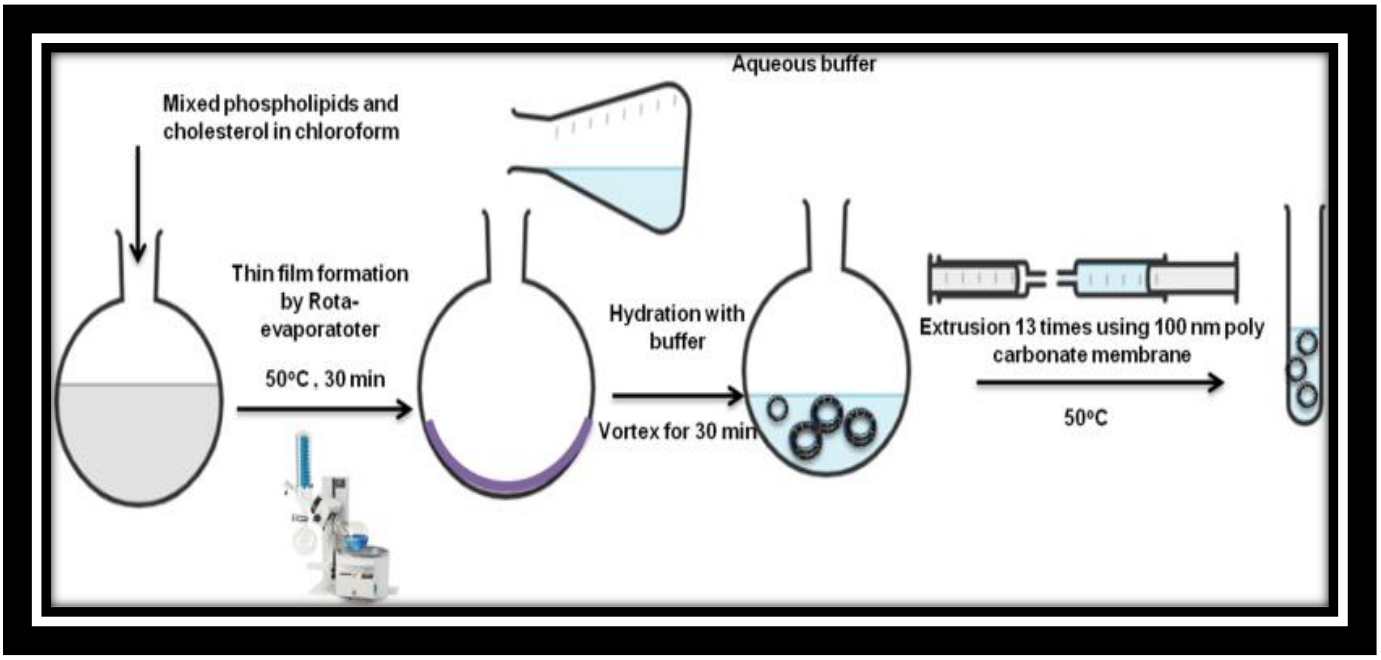

Fig 3 :-Liposomes preparation *via* thin-film hydration extrusion technique.

2.Reverse-phase evaporation method :-
By creating a water-in-oil emulsion, the reverse-phase evaporation technique is typically employed as a substitute for thin-film hydration. An aqueous buffer containing the hydrophilic medication is immediately combined with the lipids once they have been dissolved in an organic solvent. Lipid vesicles were then scattered throughout the aqueous solution as a result of the organic solvent evaporating under lower pressure in a rotary evaporator. Extrusion can decrease the produced vesicles' average size and polydispersity. High molecular weight compounds can be used using this technique, although organic solvents and sonication conditions may denature medicinal peptides.
3. Solvent injection methods :- The type of organic solvent employed was utilised to categorise the injection techniques. The hydrophobic active compounds were quickly introduced into an aqueous phase along with an organic solvent that dissolved the lipids. When mixed at a temperature higher than the solvent's boiling point, diethyl ether allows direct solvent evaporation. A 10- to 20-fold aqueous solution is needed when utilising ethanol for injection, and it can be vacuum-evaporated using a rotary evaporator, dialysis, or filtration. Higher polydispersity indexes (PDI) liposomal formulations were often produced using this technique . Furthermore, prolonged contact to organic solvents and high temperatures may decrease the stability of drugs and lipids .

4. Detergent removal method :-
Using a round-bottom flask, lipids and a high critical micelle concentration (CMC) surfactant were dissolved in an appropriate organic solvent. After the solvent gently evaporated, a thin layer formed at the flask's bottom. The lipid film was subsequently hydrated in an aqueous solution containing the drug molecules to produce a mixed micelle solution. Dialysis, size-exclusion chromatography, adsorption onto hydrophobic beads, or dilution are the next methods used to eliminate the surfactant. After solution concentration, a LUVs liposome vesicle will be created. The majority of hydrophilic medications are detached from the liposomes during the detergent removal process, which is a major disadvantage of this technique.
5.Dehydration-rehydration method :-
Sonication is an organic solvent-free approach for creating LUVs. This technique involves sonication after the lipids are directly dispersed at low concentrations into an aqueous solution containing the drug molecules. The first stage is dehydration, which involves evaporating water under nitrogen to form a multilayered film that traps the drug molecules. The drug molecules are then encapsulated in big vesicles through a hydration process. This approach is straightforward, however the liposomes' diameters vary greatly.

6. Heating method :- Additionally, it is an organic solvent-free method. Using a 3–5% hydration agent, such as glycerin or propylene glycol, lipids are directly hydrated with aqueous solution and heated for at least an hour above the Tm of the utilised phospholipids. When cholesterol is added to the formulation, the suspension can be heated to 100 °C. In order to stop nanoparticle coagulation and sedimentation, the hydrating agents serve as stabilisers and isotonizing additives. Additionally. The heating approach is an effective way to make powder inhalable liposomes since the hydration agents have a cryoprotective effect.

7.**pH jumping method** :- The pH jumping approach is another solvent-free way to manufacture liposomes. This approach breaks down MLVs into SUVs by exposing the aqueous solution of phosphatidic acid and phosphatidylcholine to a nearly four-fold increase in pH over a brief period of time. The proportion of SUVs compared to LUVs produced is determined by the ratio of phosphatidic acid to phosphatidyl choline.

8. Microfluidic channel method :- A novel technique for preparing liposomes has recently been proposed: the microfluidic channel method. A technique for using liquids in tiny channels is provided by microfluidics. This technique involves dissolving lipids in ethanol or isopropanol and injecting the resulting solution upright or in the opposite direction to the aqueous medium into

the micro-channels. This process creates liposomes by continuously mixing the organic and aqueous solutions axially. Surfactants are used to stabilise liposomes in order to prevent coagulation and separation. To produce repeatable liposomes with the appropriate average size, polydispersity, morphology, and lamellarity, microfluidic channel techniques regulate the mixing process of organic and aqueous phases.

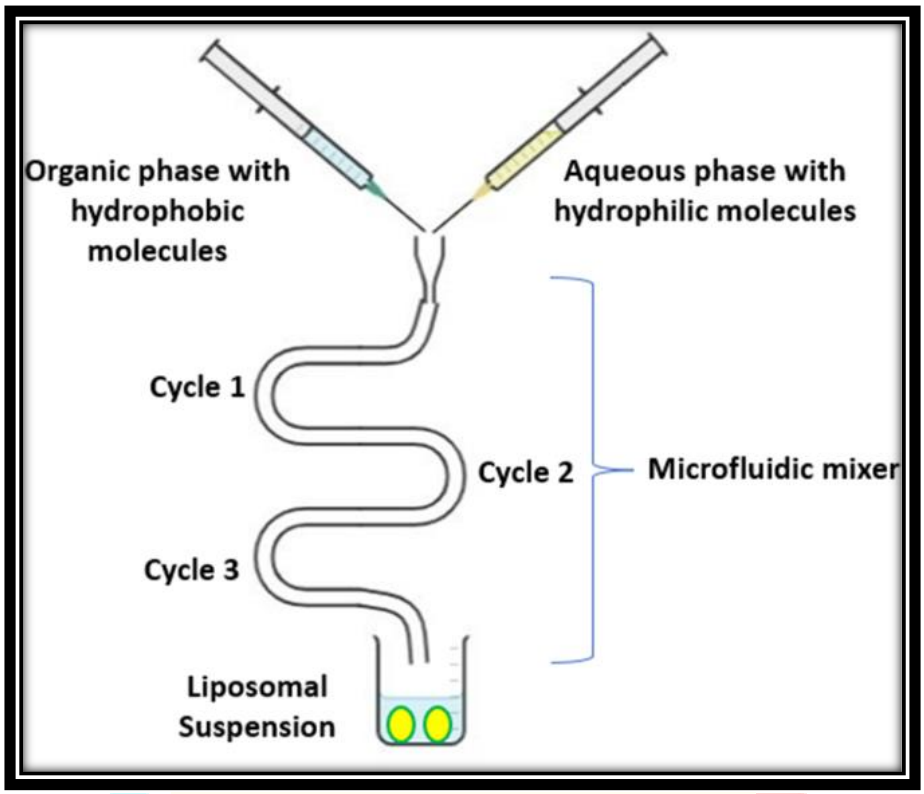

Fig 4 Schematic representation of injection methods method.

9.SUPERCRITICAL FLUIDIC METHOD :-

Instead of employing organic solvents to breakdown lipids, this approach used carbon dioxide (CO2), a supercritical fluid. Phase transition of the dissolved phospholipids is made possible by a high-performance liquid pump that continuously supplies the aqueous phase into a cell containing the supercritical lipid solution. After all CO2 has been removed, liposomes will develop at a sudden drop in pressure. This approach produced encapsulation efficiencies that were five times greater. Even with the use of inexpensive and environmentally safe carbon dioxide, this approach suffers from high cost, low yield, and unique infrastructures.

10. Post preparation handlings :-

1. Freeze-thaw cycles :- This method is typically applied while preparing liposomes in order to improve liposome lamellarity and encapsulation efficiency. This method used freeze-thaw cycles in liquid nitrogen between -196 ℃ and below the phospholipids' transition temperature.

2. Freeze-drying (lyophilization) :- Lyophilization becomes a crucial treatment for liposomes encasing thermosensitive biomolecules. Freeze-drying entails deep freezing the liposome suspension after mixing with a cryoprotective, primarily 5–10% sucrose or trehalose. After that, a sublimation step at very low temperature and reduced vacuum was applied to convert the liquid samples to fluffy solid particulates.

Properties of Liposomes :-

Because of their special qualities, liposomes—spherical vesicles made of one or more phospholipid bilayers—are utilised in medicine delivery and other applications[1]. The main characteristics of liposomes are listed below:

Biocompatibility and biodegradability :- Because they are composed of phospholipids, which are also present in biological membranes[1], liposomes are both biocompatible and biodegradable. This feature improves their suitability for medication administration and lowers the risk of toxicity[1].

Amphiphilicity :- Liposomes have both hydrophilic and hydrophobic regions. The hydrophilic core can encapsulate drugs that are soluble in water, whereas the hydrophobic bilayer can contain drugs that are soluble in lipids. This dual capability allows for the delivery of a wide range of drugs.

Size and charge variability :- Liposomes can range in size from 50 nm to several micrometres and have a neutral, positively charged (cationic), or negatively charged (anionic)[1] surface charge, depending on the composition of the phospholipids. The rate at which they enter the bloodstream and are taken up by cells depends on their size and charge.

Controlled release of encapsulated drugs :- Liposomes can be used to release encapsulated drugs gradually and under control. The composition of the liposomal membrane can be changed to control this release, as can the inclusion of stimuli-responsive components that release the medication in reaction to pH or temperature changes. Both the composition of the liposomal membrane and the usage of stimuli-responsive components that release the drug in reaction to pH or temperature changes can be used to regulate this release[1].

Low immunogenicity :- The drug's bioavailability is enhanced and its bloodstream circulation time is extended when liposomes are appropriately created[1], such as by adding polyethylene glycol (PEGylation), since they can evade the immune system and avoid being swiftly eliminated by the mononuclear phagocyte system (MPS). Consequently, the drug's bloodstream circulation period is extended and its bioavailability is enhanced[1].

Encapsulation efficiency :- Pharmaceuticals that are hydrophilic, hydrophobic, or amphiphilic can[1] be effectively encapsulated by liposomes. As a result, they can provide a range of therapeutic agents with increased adaptability, improving the stability and solubility of medications and reducing toxicity.

Enhanced permeability and retention (EPR) effect :- Liposomes can accumulate in tumour tissues due to their enhanced permeability and retention impact. Liposomes can efficiently and passively target tumour areas and deliver anticancer drugs since the vascularization of tumours is frequently more permeable than that of healthy tissues [1].

- **LIPOSOMES CHARACTERIZATION :-**

Average size and size distribution (also known as polydispersity index (PDI)), surface charge (also known as Zeta potential), shape and morphology, lamellarity, encapsulation efficiency, phase behaviour (also known as polymorphism), and in vitro release profile are all examples of liposome physiochemical characterisation.

Represent different techniques used for the assessment of liposome parameters.

Liposomes characteristics	Characterization technique
Average particle size	Dynamic light scattering (DLS) and microscope technology: Scanning and transmission electron microscopy (SEM/TEM), cryogenic-TEM (Cryo-TEM), and atomic force microscopy (AFM)
Zeta potential/Surface charge	Electrophoretic mobility, DLS
Particle shape/morphology	TEM, Cryo-TEM, and AFM
Lamellarity	Cryo-TEM and ^{31}P-NMR
Phase behavior	X-ray diffraction (XRD), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)
Encapsulation efficiency/Drug release	Centrifugation, dialysis followed by drug content determination using chromatographic and/or spectrophotometric methods

- **Protein corona fingerprintes of liposomes :-** Numerous issues related to the poor efficacy of anticancer medications have been addressed by liposomes. A theory has recently surfaced that the limited effectiveness of liposomal medications in clinical practice is caused by a lack of understanding of liposome behaviour in vivo. In vivo, plasma proteins often cover lipid vesicles, creating a biomolecular coating known as the protein corona (PrC). According to recent research, PrC fingerprints (PrCFs) improved liposome adhesion to cancer cells, resulting in effective particle internalisation and localisation .
- **Targeting liposomes to specific organelles** :- The ability to target drugs to specific organelles is a sub-area of growing interest related to active targeting covered in the section on stealth liposomes. While specific subcellular targeting remains a significant challenge, efforts have so far been most successful with targeting drugs to lysosomes or mitochondria; most of these systems are still in the in vitro research phase. In one such in vitro demonstration, drugs encapsulated in liposomes modified with various lysosomotropic ligands, such as octadecyl-rhodamine B (RhB). Targeting medications to lysosomes or mitochondria has proven to be the most successful approach thus far, although exact subcellular targeting remains a considerable difficulty. The majority of these systems are still in the in vitro stage of development. Drugs encapsulated in liposomes modified with different lysosomotropic ligands, like octadecyl-rhodamine B (RhB), were successfully transported to lysosomes in one such in vitro demonstration (Meerovich et al., 2011). In other studies, the polymer (Rh123)-PEG-DOPE (Rhodamine 123-Polyethylene glycol-1,2-dioleoyl-sn-glycero-3-phosphoethanolamine), which contains the mitochondriotropic dye rhodamine, was used to target mitochondria in vitro (Biswas et al., 2011). The polymer was well absorbed by cells (HeLa, B16F10) and accumulated to a high degree in the

mitochondria when it was integrated into the liposomes' lipid bilayer. Compared to non-targeted liposomes or free PCL, these mitochondrial-targeted liposomes exhibited increased cytotoxicity toward cancer cells when loaded with PCL. In order to design medications and delivery vehicles with strong stability, pharmacokinetic and pharmacodynamic profiles, and good biocompatibility and biodegradability, it is necessary to comprehend the microenvironment of the diseased site. Such subcellular targeting is highly desirable from a pharmaceutical standpoint.

Improving delivery of poorly soluble drugs: pharmacosomes :-

Pharmacosomes have gotten less attention than their counterparts since they were first reported in the 1980s, in part because of their more specialised uses and more difficult construction methods. According to Semalty et al. (2009), pharmacosomes are amphiphilic phospholipid complexes of medications that attach to phospholipids by covalent, electrostatic, or hydrogen bonding. They are believed to increase the bioavailability of medications that are both poorly lipophilic and poorly water soluble. Pharmacosomes can exist as hexagonal aggregates or ultrafine micelles depending on their chemical structure (Shivhare et al., 2013). While other vesicles, like ethosomes and transferosomes, can be made using simple liposome assembly techniques, pharmacosomes frequently require complexation steps to achieve the required drug-lipid complex; these methods are often specific to the type of drug that is complexed to the phospholipid. Once prepared, however, pharmacosomes tend to show a significantly better dissolution profile than free drug; in one recent example, aceclofenac pharmacosomes showed an almost 10% better dissolution profile than aceclofenac acid (Semalty et al., 2010). Assembly techniques are frequently unique to the kind of medication that is complexed with the phospholipid. However, once prepared, pharmacosomes typically exhibit a much better dissolution profile than free drug. In a recent example, aceclofenac pharmacosomes demonstrated a dissolution profile that was nearly 10% better than aceclofenac acid (Semalty et al., 2010) based on several analytical in vitro measurements, including in vitro dissolution. In comparison to free acid, the pharmacosomes' solubility was also enhanced. Pharmacosomes are typically made by solvent evaporation after the drug complexation stage. To create the aqueous phase pharmacosomes, the dried powder that represents the pharmacosomes is rehydrated in an aqueous buffer after the solvent has evaporated. For several non-steroidal anti-inflammatory, cardiovascular, and antitumor medications, pharmacosomes have been made. The size and functional groups of the drug molecule, the length of the lipid chain, and the spacer are the main factors that determine the pharmacosomes' in vivo pharmacokinetic behaviour and rate of distribution of the active drug molecule without the lipid carrier after absorption (Sharma et al., 2014). Recently, medications like ketoprofen (Kamalesh et al., 2014) have been encapsulated inside pharmacosomes with impressive results in in vitro laboratory studies: according to analytical data, the solubility of ketoprofen was 93.3% compared to that of free ketoprofen (49.77%).
In vitro experiments have demonstrated that furosemide-bound pharmacosomes have a permeability of the encapsulated medication that is more than 28% higher than that of free furosemide (Chatap et al., 2014).

Stimuli-responsive liposomes and nebulized liposomes :- There have been two primary categories of triggers investigated: local triggers like pH and enzymes, and remote triggers like heat, ultrasound, and light (Bibi et al., 2012; Puri, 2014). Despite an increasing amount of research, these stimuli-responsive liposomes have shown to be quite disappointing in real-world applications. Nevertheless, a few systems—mostly thermosensitive liposomes—have advanced to clinical testing. Phase II and III human clinical trials are currently underway for the thermosensitive liposomal formulation ThermoDox (Celsion Corporation, Lawrenceville, NJ), which contains lysophosphatidylcholine and is intended to treat a variety of cancers, including primary liver cancer, recurrent chest wall breast cancer, colorectal, pancreatic, and metastatic liver cancer. Research is being conducted to further enhance the drug's efficacy and raise its chances of success. Nebulised liposomes have also made their way into clinical settings. One such formulation for delivering nebulised amikacin to the lungs is Insmed's liposomal amikacin (Arikace) (Li et al., 2008). Amikacin is encapsulated in sustained-release liposomes containing phospholipids (DPPC) and cholesterol in this formulation. The formulation is presently conducting clinical studies for the treatment of M. avium infection, and the clinical trials for the use of these liposomes for the treatment of cystic fibrosis patients with persistent Pseudomonas aeruginosa lung infection have finished.

The Way Liposome Work :- An aqueous solution encased in a hydrophobic membrane is called a liposome. Because hydrophobic substances are readily absorbed by lipid membranes, liposomes can contain both hydrophilic and hydrophobic molecules. A medication's lipid content and other physiochemical characteristics will determine how far it is positioned. Liposomal contents are released when lipid bilayers merge with other cell bilayers (the cell membrane), which then transport the necessary drug molecules to the site of action. Bilayers are produced as a result of the following factors:

- Folding into tight, circular vesicles can reduce unfavourable interactions between the hydrophilic and hydrophobic phases.
- Because spherical shapes have the least surface tension and are the most stable, the development of large vesicles reduces the tremendous free energy differential between the hydrophilic and hydrophobic environments. As a result, the self-assembling structure that produces vesicles is as stable as possible.

How to use liposomes to give medication:

Adsorption :- Liposomes adhere to cell membranes through a process called adsorption.

Endocytosis :- liposomes' internalisation and engulfment following their adsorption on the cell membrane.

Fusion :- The contents of liposomes are transported straight to the cytoplasm when liposomal lipid bilayers combine with the lipoidal cell membrane through lateral diffusion and lipid intermingling.

Lipid Exchange :- Lipid transfer proteins in the cell membrane are able to identify liposomes and start lipid exchange because the phospholipids in the cell membrane and the liposomal lipid membrane are comparable.

For instance, in order to meet their needs for rapid development, cancer cells must absorb massive amounts of fat. Additionally, they see liposomes—which contain anticancer medications—as a possible food source. They are absorbed when they are targeted by liposomes. As soon as cancer cells escape the liposome and reach the site, anticancer drugs eliminate them.

Advantages of Liposomes :-

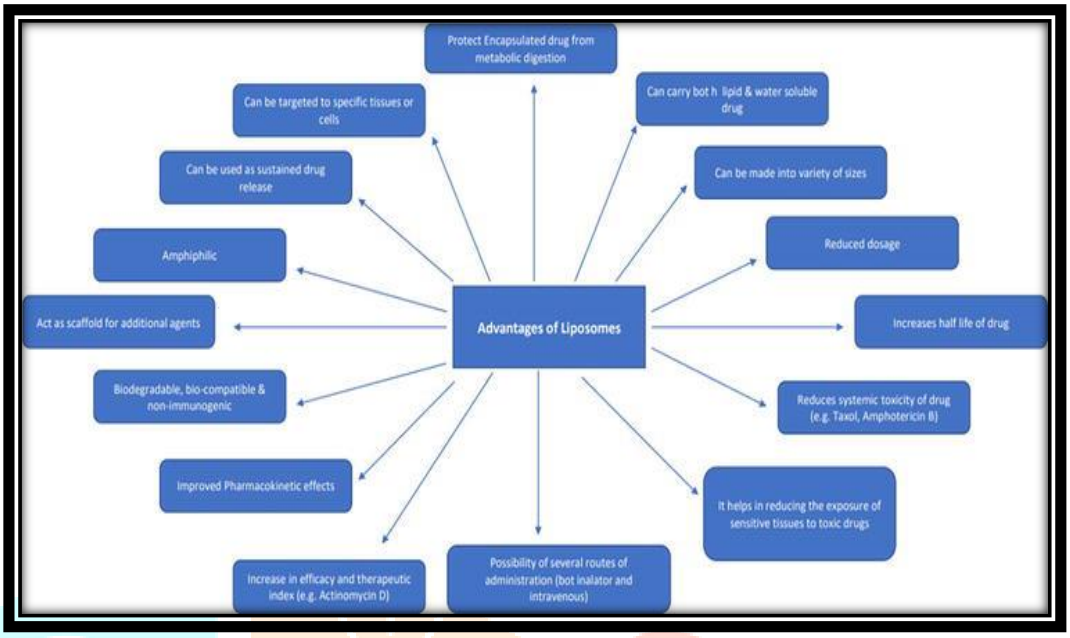

Fig 5 :- Advantages of Liposomes

Both water-soluble and insoluble medicines are trapped by amphipathic properties.

- It provides tailored medication delivery
- Enhanced medication efficacy and therapeutic index
- Non-ionic
- Liposomes lessen the exposure of delicate tissues to harmful medications.
- Gives tumour tissue selective passive targeting.
- Prevent medication oxidation
- Liposomes are biodegradable.
- Biocompatible
- Liposomes improve the drug's stability.
- Site avoidance effect[2]
- Improve protein stabilization[2]
- Provide sustained release[2]
- Direct interaction of drug with cell[2]
- Site avoidance effect[2]

Disadvantages of Liposomes:[2]

- Low solubility
- Short half-life
- Production cost is high
- Leakage and fusion of encapsulated drug
- may occur
- Oxidation of phospholipids may occur
- Allergic reactions may occur to liposomal constituents
- Less stable[2]

VI. APPLICATION OF LIPOSOMES :-

Pharmaceutical uses for liposomes in oral and transdermal drug delivery systems are excellent. This drug delivery [2] method increases the efficacy of medications while lowering their harmful effects. By attaching amino acid fragments that target particular receptor cells, the liposome is directed to the location of action. The liposomal drug delivery system has been suggested for a number of drug delivery applications, some of which are listed below:

1. Enhancement of Solubilisation (Amphotericin-B, Paclitaxel) [2]

2. Protection of sensitive drug molecules (Cytosine arabinose, DNA, RNA, Ribozymes) [2]

3. Enhancement of intracellular uptake (Anticancer, antiviral and antimicrobial drugs)[2]

4. Alteration in pharmacokinetics and biodistribution (prolonged or SR drugs with short circulatory half-life)[2]

Several recent applications of liposomal drug delivery system are as follows[2]

A. Liposome for Respiratory Drug Delivery System[2]: Liposomes are frequently utilised to treat a variety of respiratory conditions. Liposomal aerosols can be designed to lower toxicity, increase stability, avoid local irritation, and achieve continuous release. The composition, size, charge, drug/lipid ratio, and drug delivery technique should all be taken into account while creating liposomes for lung distribution.

During nebulisation, the liquid or dry form is inhaled. Spray drying or milling are two methods used to create drug powder liposomes.

B. Liposomes in Ophthalmic Disorders: Liposomes have been shown to have positive effects for a number of eye conditions, including dry eyes, keratitis, corneal transplant rejection, uveitis, endophthalmitis, and proliferative vitro retinopathy. Recently, a liposomal formulation of the medication verteporfin which has been shown to be useful against eye disorders was approved.

C. Liposome as Vaccine Adjuvant: Liposomes are a well-established immune adjuvant that enhances both cell-mediated and noncell-mediated immunity.[1] Liposomal immuno-adjuvant works through both passive buildup in the local lymph node and the gradual release of encapsulated antigen upon intramuscular injection.[1] The liposome can either integrate antigens into the bilayers or hold them in the aqueous cavity, depending on how lipophilic they are.

With the aid of phosphotidyl serine, the targeting of liposomes causes them to accumulate in lymphoid tissue. Microbes, soluble antigens, and deoxyribonucleic acid cytokinesis can all be inoculated with liposomes to create the liposomal vaccine.

D. Liposomes for Brain Targeting: Because liposomes are biodegradable and biocompatible, they are utilised in brain drug delivery systems. Both large-diameter and small-diameter liposomes diffuse freely across the blood-brain barrier. However, receptor-mediated or absorptive-mediated transcytosis may be used to move tiny unilamellar vesicles (SUVs) attached to brain drug transport vectors across the blood-brain barrier. When administered systemically, the neuropeptides leuenkephaline and mefenkephalin kyoforphin typically do not cross the blood-brain barrier (BBB), but the antidepressant amitriptyline typically does because of the versatility of this method. Cationic liposomes undergo absorptive mediated endocytosis into cells, whereas the same undergoing absorptive mediated transcytosis through the BBB has not yet been determined. Liposomes coated with mannose reach the brain and assist the transport of loaded drug[1]. Mannose-coated liposomes enter the brain and help move the medication through the blood-brain barrier. When administered systemically, the neuropeptides leuenkephaline, mefenkephalin, and kyoforphin typically do not penetrate the blood-brain barrier. Because of this method's adaptability, the antidepressant amitriptyline typically crosses the blood-brain barrier.

E. Liposome as Anti-Infective Agents: The drug-using liposomal carrier can be used to treat diseases such as leishmaniosis, candidiasis, aspergillosis, histoplasmosis, erythrocytosis, gerardiasis, malaria, and tuberculosis[1].

F. Liposome in Cancer Therapy: When used long-term, all cancer medications have severe hazardous side effects. With fewer harmful effects, the liposomal method targets the medicine to the tumour. Because they can circulate over a longer period of time, the small and stable liposomes are passively targeted to the various tumours. These days, a lot of herbal anti-cancer medications are also packaged into liposomes for improved targeting and increased absorption.

G. Liposomes as Protein Drug Delivery: They are employed to improve the solubilisation of drugs.

H. Liposomes in Cosmetics: Their physiology is comparable to that of the cell membrane, and they release things into the cells, which is why they are utilised in cosmetics.

I. Liposomes in Intracellular Drug Delivery[1]: pharmaceuticals having intracellular receptors must penetrate the plasma membrane in order to exhibit pharmacological activity. Because liposomes may hold higher drug concentrations than extracellular fluid, liposomal delivery of pharmaceuticals that typically enter cells by pinocytosis can be particularly successful. Because liposomes can hold higher drug concentrations than extracellular fluid, liposomal delivery of medications that typically enter cells by pinocytosis can be quite successful. Negatively charged liposomes are mostly taken up by cells through the endocytosis process, which is more effective than pinocytosis. Liposomes can be utilised to boost the cytosolic delivery of several medications that are often poorly absorbed into cells.

Certain medications that are typically poorly absorbed by cells can have their cytosolic delivery increased by using liposomes.[1]

J. Liposomes in Sustained Release Drug Delivery: It is frequently necessary to take sustained release drug delivery systems multiple times a day in order to reach and then maintain the concentration of drug supplied within the therapeutically effective range required for therapy. This causes the medication level to fluctuate, which leads to unwanted toxicity and ineffectiveness. To reduce this fluctuation, new drug delivery methods, including as liposomes and niosomes, have been created.

K. Liposomes in Gene Therapy[1]: Liposomes have been extensively employed for medication and gene delivery as well as in the analytical sciences. A number of systemic illnesses are brought on by a deficiency of enzymes or other components that result from defective or absent genes. Recent years have seen a number of attempts to transfer the necessary exogenous DNA or genes to cells in order to re-establish gene expression.

Anionic liposomes have been mostly limited to the delivery of various therapeutic macromolecules, whereas cationic (and neutral) lipids are usually utilised for gene transport due to the polyanionic nature of DNA.

Lipofectin, cytofectin, lipofectamine, and transfectace are a few commonly used cationic liposome formulations.

Disease

	Liposomal drug	**Clinical applications**	**Outcome**	**References**
Systemic Fungal Infections	*AmBisome* (Liposomal Amphotericin B)	Treatment of cryptococcosis and candidiasis	Decreased nephrotoxicity and improved antifungal efficacy	[1]
Kaposi's Sarcoma	*Doxil* (Liposomal Doxorubicin)	Treatment of AIDS-related Kaposi's sarcoma	Improved tumour targeting and reduced systemic toxicity	[1]
Rheumatoid Arthritis	Liposomal Prednisolone	Anti-inflammatory therapy	Reduced inflammation with fewer side effects	[1]
Alzheimer's Disease	Liposomal Curcumin	Cognitive enhancement in Alzheimer's patients	Better brain penetration and reduced amyloid plaques	[1]
Breast Cancer	*Mylotarg* (Liposomal Gemtuzumab Ozogamicin)	Treatment of HER2-positive breast cancer	Enhanced targeting of cancer cells, leading to better outcomes	[1]
Hepatitis A	Liposomal Hepatitis A Vaccine	Preventive vaccine for hepatitis A infection	Enhanced immune response and prolonged protection	[1]
Cardiovascular Disease	Liposomal Statins	Targeted delivery for atherosclerosis management	Reduced plaque size and inflammation with fewer side effects	[1]
Pancreatic Cancer	Liposomal Irinotecan (*Onivyde*)	Treatment of metastatic pancreatic cancer	Improved overall survival and progression-free	[1]

Disease	Liposomal drug	Clinical applications	Outcome	References
			survival compared to standard therapy	
Triple-Negative Breast Cancer	Liposomal Doxorubicin and Cyclophosphamide	Treatment of early-stage triple-negative breast cancer	Higher pathological complete response and better tolerability than free drugs[1]	[1]
Non-Small Cell Lung Cancer (NSCLC)	Liposomal Cisplatin	Treatment of advanced NSCLC	Reduced nephrotoxicity and enhanced efficacy compared to free cisplatin	[1]
Ovarian Cancer	*Doxil* (Liposomal Doxorubicin)	Treatment of advanced ovarian cancer	Reduced cardiotoxicity and prolonged drug circulation	
	Liposomal Paclitaxel	First-line treatment for ovarian cancer	Increased tumour response rate and reduced peripheral neuropathy compared to free paclitaxel	
Colorectal Cancer	Liposomal Irinotecan (*Onivyde*) plus Fluorouracil and Leucovorin	Second-line treatment for metastatic colorectal cancer	Significantly improved survival compared to other irinotecan formulations	
Glioblastoma	Liposomal Temozolomide	Treatment of recurrent glioblastoma	Enhanced brain tumour penetration and improved survival rates in clinical trials	[1]
HIV/AIDS (Kaposi's Sarcoma)	*Doxil* (Liposomal Doxorubicin)	Treatment of Kaposi's sarcoma in HIV patients	Reduced systemic toxicity and prolonged drug exposure	[1]
Prostate Cancer	Liposomal Docetaxel	Treatment of castration-resistant prostate cancer	Increased median survival and improved quality of life	

Disease	Liposomal drug	Clinical applications	Outcome	References
Hepatocellular Carcinoma	Liposomal Doxorubicin	Advanced hepatocellular carcinoma treatment	Higher drug concentration in tumours with fewer side effects	[1]

VII. ADVANCEMENTS IN LIPOSOMES:

Ethosomes :- They are effective at delivering[1] 30% ethanol and soy phosphatidylcholine to the skin.

Immuno Liposomes: Antibodies were used to alter them.

Niosomes:-These are tiny, nonionic surfactant-based unilamellar vesicles.

Stealth Liposomes: They are a novel class of liposomes designed[1] to increase stability and extend their half-life in circulation.

Polyethylene glycol (PEG) should be used to coat liposomes in order to prepare them.

They are a novel class of liposomes designed to increase stability and extend their half-life in circulation. Polyethylene glycol (PEG) should be used to coat liposomes in order to prepare them.

VIII. CONCLUSION :-

Liposomes are a major advancement in drug delivery systems because they guarantee better bioavailability of the therapeutic agents, their selective delivery, and their reduced toxicity. In addition to encapsulating hydrophilic drugs, their ability to encapsulate hydrophobic drugs, coupled with their excellent biocompatibility, makes them versatile carriers for a wide range of pharmaceutical applications[1]. While stability, scalability, and cost-effectiveness are still major challenges, the field o They are adaptable carriers for a variety of pharmaceutical applications due to their exceptional biocompatibility and capacity to encapsulate both hydrophilic and hydrophobic drugs. Ongoing research and technological advancements in the field of liposomal medicines continue to increase their potential, even though major obstacles including stability, scalability, and cost-effectiveness still exist. Liposomes have the potential to revolutionise treatment outcomes and individualised medicine for a wide range of medical specialities as they continue to advance.

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