IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# "Advance In Drug Delivery System Based On Liposome -Composite Hydrogel Microsphere"

[1]Ms. Anjali P. Nanaware, [2]Ms. Mohini B. Yadav, [3]Dr. Vijaykumar Kale, [4]Dr. Mahesh Thakare, [5]Mr. Vaibhav Narwade

[1]Student, [2]Assistant Professor, [3]Professor, [4]Associate Professor, [5]Assistant Professor

[1]Department of B.pharm,

[1]Kasturi Shikshan Sanstha college of Pharmacy, Shikrapur, India.

***Abstract:*** Hydrogels, with their distinctive three-dimensional networks of hydrophilic polymers. Drive innovations across various biomedical applications. The ability of hydrogels to absorb and retain significant volumes of water, coupled with their structural integrity and responsiveness to environmental stimuli, renders them ideal for drug delivery, tissue engineering, and wound healing. This review delves into the classification of hydrogels based on crosslinking methods, providing. Insights into their synthesis, properties, and applications. Their potential in personalized medicine and regenerative healthcare solutions.

**Keyword** - Hydrogel Drug Delivery, Oral, Injectable, Topical, Ocular

## I. INTRODUCTION:

Conventional drug delivery systems have inherent limitations such as poor targeting and low therapeutic indices, which result in systematic side effects and increase costs and Duration of the therapy. To overcome these drawbacks, various Nano delivery systems Have been developed for different therapeutic applications. Among them, liposomes (self- Assembled lipid vesicles) are, to date, one of the most studied Nano systems for clinical Application. they can Also provide excellent biocompatibility, safety and controlled drug release kinetics.[1,2,3,]

### Liposome:

A liposome is a tiny, spherical vesical made up of one or more phospholipid bilayers surrounding an aqueous core.

As mentioned above, liposomes are biodegradable, biocompatible, nontoxic and. They are composed of amphiphilic non-immunogenic compounds (such as cholesterol and Phospholipids). They are able to improve solubility and tissue penetration of both lipophilic and hydrophilic drugs. These features have allowed their successful exploitation in Numerous areas of Nano medicine, and, at present, twenty liposome-based formulations have Been approved by the FDA (US Food and Drug Administration) and/or EMA (European Medicines Agency. they can deliver higher drug concentrations in transdermal applications [4,5,]

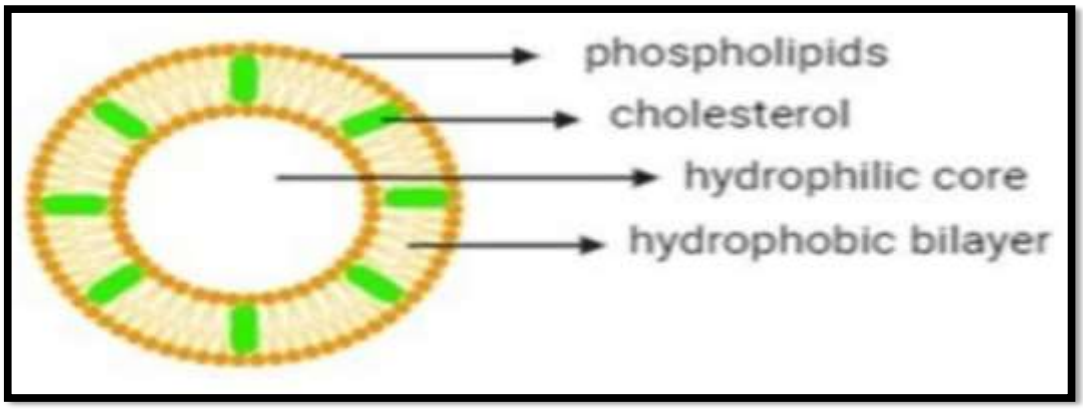


**Figure No:1 The general structure of liposome.**

**Classification of Hydrogel:**

The classification of hydrogels can be based on various criteria, including their source, cross-linking methods, composition, degradability, stimuli responsiveness, and ionic charge. In this context, we categorize them into physical and chemical hydrogels, distinguished by their cross-linking formation mechanisms, as illustrated in Figure 2. Hybrid gels featuring both physical and chemical cross-linking are not individually classified here. We proceed to select and review various representative hydrogels characterized by diverse gelation mechanisms.

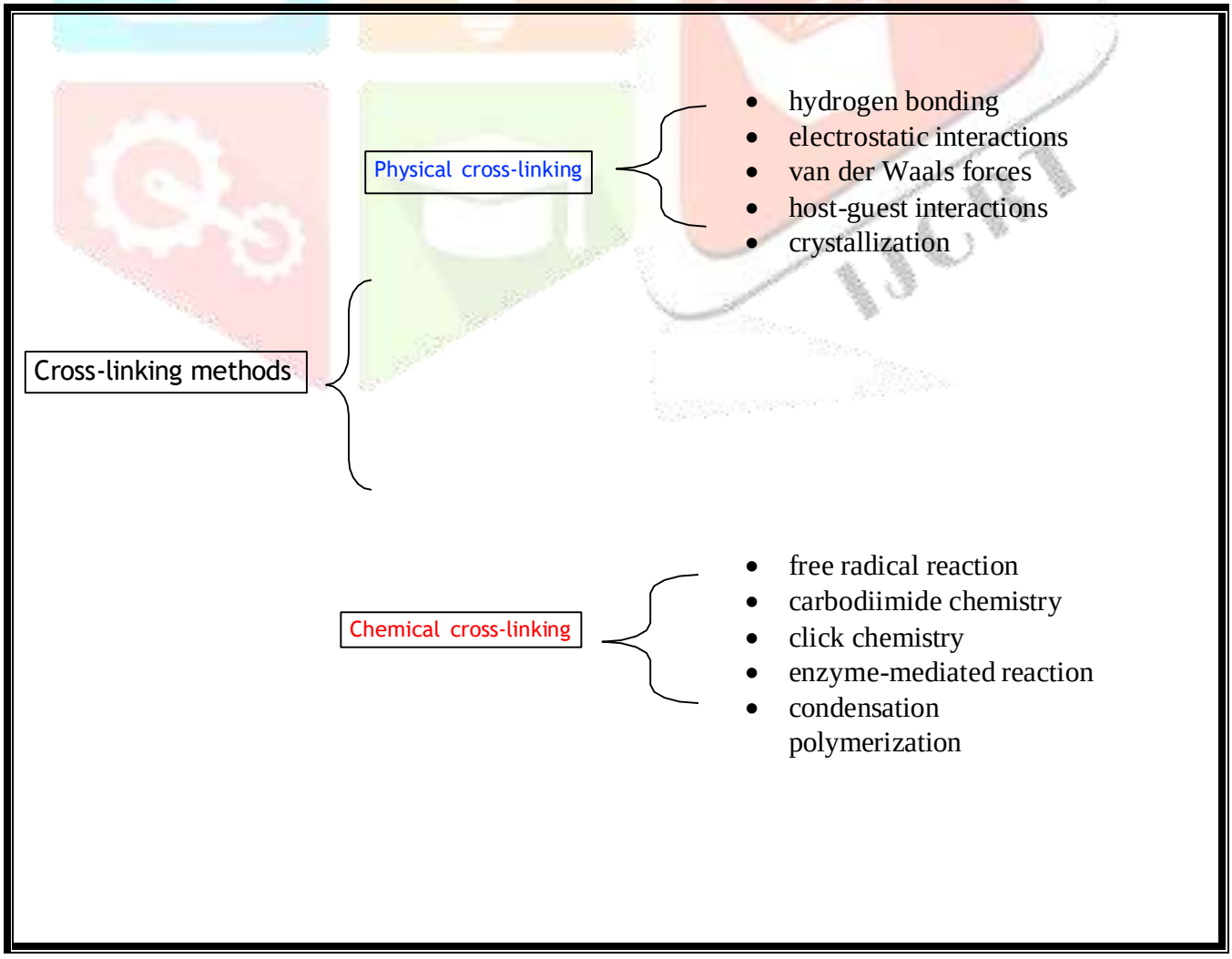


**Figure No: 2 Classification of hydrogel based on the cross-linking fromation mechanism.**

**1. Physical hydrogels:**

Physical hydrogels are synthesized from low-molecular-weight compounds or poly-Mars through non-covalent interactions such as hydrogen bonding van der Waals Forces electrostatic attractions and specific host-guest interactions These reversible interactions allow physical gels to undergo gel-to-sol transitions in response to environmental stimuli like temperature, pH, and ionic strength, endowing them with adaptability and responsiveness. In contrast to chemical gels, which rely on permanent Covalent bonds, physical gels form transient networks through weak, albeit numerous, Physicochemical bonds, granting them properties such as softness, reversibility, sensitive to external stimuli. like temperature, pH, and ionic strength, endowing them with adaptability and responsiveness. In contrast to chemical gels, which rely on permanent Covalent bonds, physical gels form transient networks through weak, albeit numerous, Physicochemical bonds, granting them properties such as softness, reversibility, sensitive to external stimuli. These features make physical gels particularly suitable forApplications requiring sensitivity to environmental changes, such as in drug delivery and Tissue engineering scenarios. Numerous physical hydrogels have been designed for use Drug delivery applications, with several notable examples listed bel Sun etal. exploreda novel hydrogel formulation integrating nanostructured lipid. Carriers (NLC) with chitosan-thiophosphates (chitosan-TPP) hydrogel beads, leveraging Hydrophobic interactions for effcient encapsulation of hydrophobic active substancesThe chitosan-TPP hydrogel forms through electrostatic interactions between the phosphate Groups of TPP and the protonated amino groups of chitosan. This strategy not only Improves bioavailability and controlled drug release but also holds signifcant promise for enhancing topical drug delivery systems, illustrating the potential of hydrophobic Interactions in innovative hydrogel designs.

**2. Chemical hydrogel:**

Chemical hydrogels, synthesized through covalent bonding of polymers, leverage Chemically active for crosslinking, utilizing a variety of methods such as carbonic- chemistry, Free radical Polymerization, and click chemistry These approaches offer chemical hydrogels enhanced matrix stabilization and greater Troll over gel formation, enabling a higher degree of flexibility and spatiotemporal precision Than physical gels. Specifcally, enzymatic crosslinking, utilizing biocompatible enzymes Like peroxidases and transglutaminases, presents a favorable method for creating biocom- Patible, nonimmunogenic hydrogels suitable for tissue engineering, drug delivery, and Regenerative medicine (TERM) applications due to its mild reaction conditions and minimal Cytotoxicity Additionally, electron irradiation techniques have emerged, providing Effcient and precise crosslinking capabilities that expand the possibilities for hydrogel Customization. The pioneering synthesis of pHEMA hydrogels by Wichterle and Lim, achieved Through free radical polymerization, highlights the potential for integrating acrylatederived Acid transforming them into cross-linked hydrogels. Similarly, high-energyAction, including gamma rays and electron beams, facilitates the transformation of vinyl Polymer solutions into hydrogels or initiates the polymerization of monofunctional acry- Lates with cross-linkers, forming hydrogels. This process involves radical generation from carbonhydrogen radicals, which then recombine To create covalent cross-links. Specifcally, polyvinyl alcohol, polyethylene glycol, andPolyacrylic acid are capable of undergoing such radical reactions, facilitating the formation of hydrogels [6,7,8,]

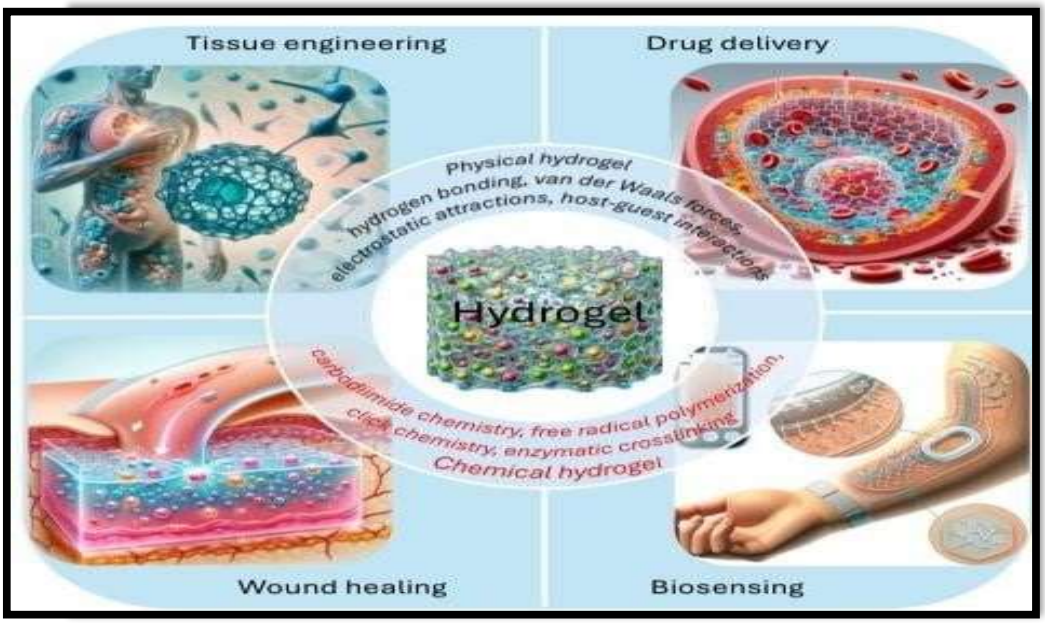


**Figure No: 3 Illustration of hydrogel classification based on cross-linking method and their biomedical application.**

**Advantages:**

1. Drug Administration protocols may be simplified.
2. Toxicity is reduced by delivering a drug to its target site there by Reducing harmful systemic effect.
3. Drug can be Administered in a smaller dose to produce the desired effect.
4. Avoidance of hepatic frist pass metabolism.
5. Enhancement of the Absorption of target molecule. such as peptides and particulate.

**Disadvantages:**

1. Rapid clearance of targeted system.
2. Immune Reaction against intravenous Administered carrier system.
3. In sufficient localization of targeted system in to tumour cell.
4. Diffusion and Redistribution of released drug.
5. Requires Highly sophisticated technology for the formulation.

**Preparation of Liposome and LHMs:**

Liposome Are Vesicular Structure Formed Through the Hydration of Phospolipid Molecules, Which Self-Assemble in an Aqueous phase to Create Bilayer Structure. Liposome Are classified into unilamellar and multilamellar vesicles based on the number of lipid bilayers and the presence of a shared aqueouous core. Their size typically ranges from tens of nanometers to several micrometers depending on the preparation method employed [9,10,11]

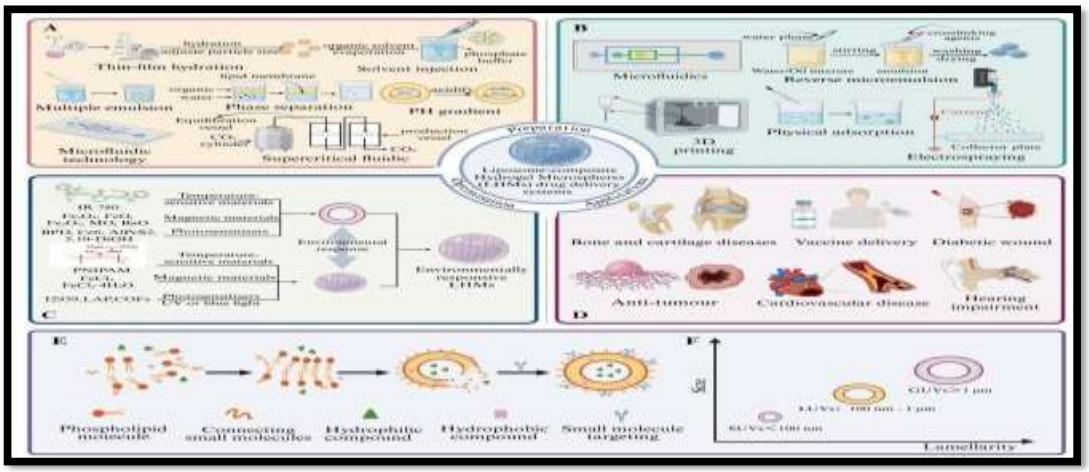


**Figure No: 4 Schematic of the preparation methodology, optimization process, and applications of LHMS as drug delivery systems.**

**Method Of Preparation:**

1. Thin-film Hydration Method
2. Solvent injection Method
3. Multiple Emulsion Method
4. Reverse-Phase Evaporation
5. Gradient Method
6. Freeze-Drying Method
7. Supercritical Fluidics Technology
8. Microfluidic Technology

**1. Thin -Film Hydration Method:**

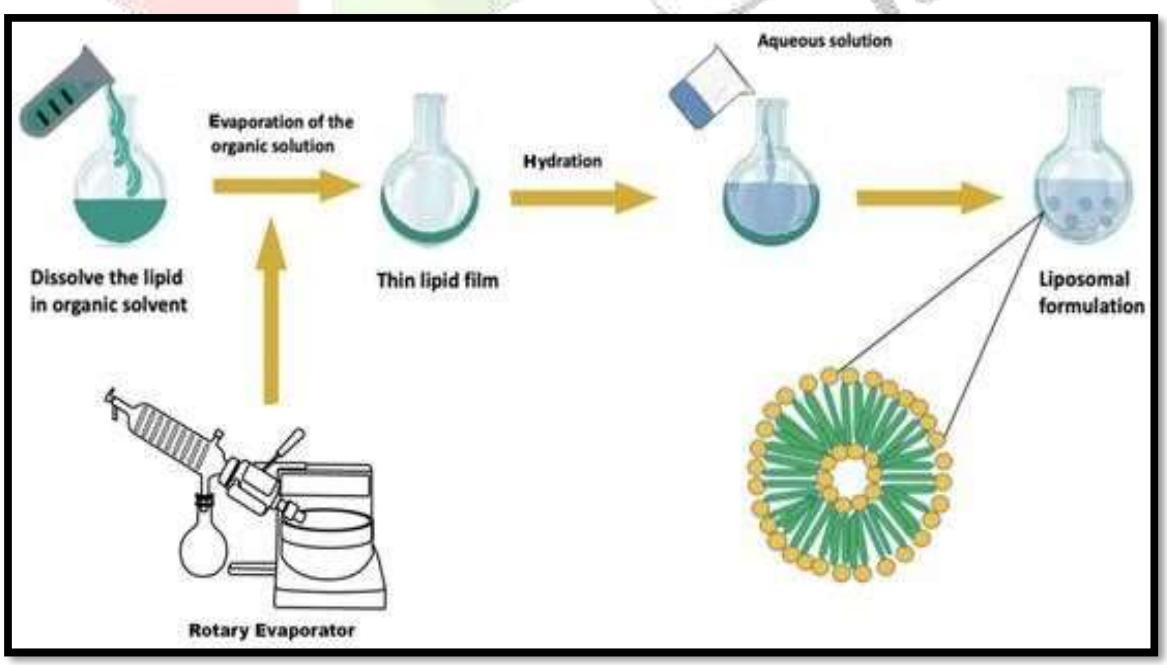


**Figure No:5 thin film hydration method.**

Thin-film hydration method. The thin-film hydration method is widely employed in laboratory settings for liposome preparation owing to its operational simplicity. In this process, phospholipids, cholesterol, other lipid components, and the target drug are initially dissolved in an organic solvent system, typically comprising chloroform, methanol, and/or ethyl ether. Subsequently, a homogeneous lipid film is formed on the inner surface of a rotary evaporation flask through solvent removal under reduced pressure. Upon the addition of the aqueous-phase medium and subsequent rotation under controlled conditions, the lipid film undergoes hydration, resulting in liposome formation. Although this method offers procedural simplicity, it is characterized by certain limitations, including heterogeneous particle size distribution and relatively low drug encapsulation efficiency.In addition, the type of organic solvent, the type and proportion of surfactant, the cholesterol content, the time, and the temperature of mixing affect the properties of liposomes. For instance, the physical characteristics of liposomes demonstrate substantial dependence on the solvent system employed. Specifically, the utilization of a chloroform-ether binary solvent system tends to produce LUVs, while the application of pure chloroform often results in smaller multilamellar vesicles.

**2.Solvent injection method:**

Solvent injection method. Solvent injection techniques include ether and ethanol injection methods. When similar operational principles are shared, these methods are distinguished by the choice of organic solvent. In the ether injection approach, phospholipids, cholesterol, and the target drug are dissolved in the ether. The resulting organic phase is then gradually introduced into a preheated phosphate buffer (50–60 C) under continuous magnetic stirring. The subsequent evaporation of ether facilitates the formation of drug-loaded liposomes. The ethanol injection method employs ethanol as the solvent, where the organic phase is injected into the aqueous phase to form liposomes. Residual ethanol contributes to drug stabilization and encapsulation. This compound specifically targets intestinal epithelial cells as an effective pyroptosis inhibitor, thereby preventing pyroptotic cell death in the intestinal epithelium. This protective mechanism facilitates mucosal repair in patients with ulcerative colitis, effectively reducing intestinal inflammation and promoting tissue integrity restoration.

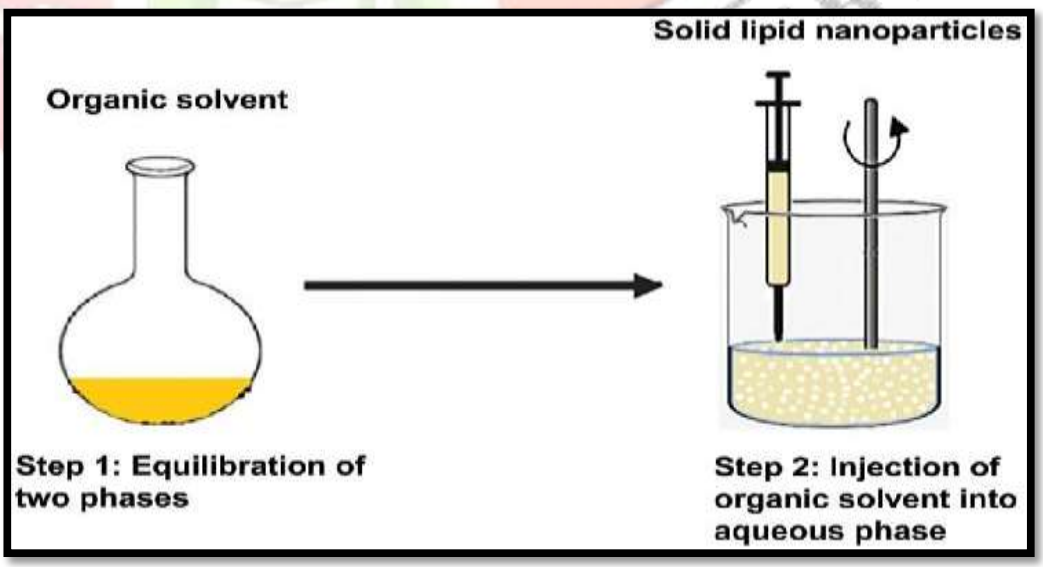


**Figure No: 6 solvent injection method.**

### 3. Multiple Emulsion Method:

Multiple emulsion method. The multiple emulsion method is fundamentally based onthe formation of a multilayered emulsion system achieved by dispersing the primary emulsion (commonly referred to as colostrum) in a distinct continuous phase. These systems are characterized as highly dispersed, as well as multi-phase structures with heterogeneous particle size distributions. Among the various types of multiple emulsions.

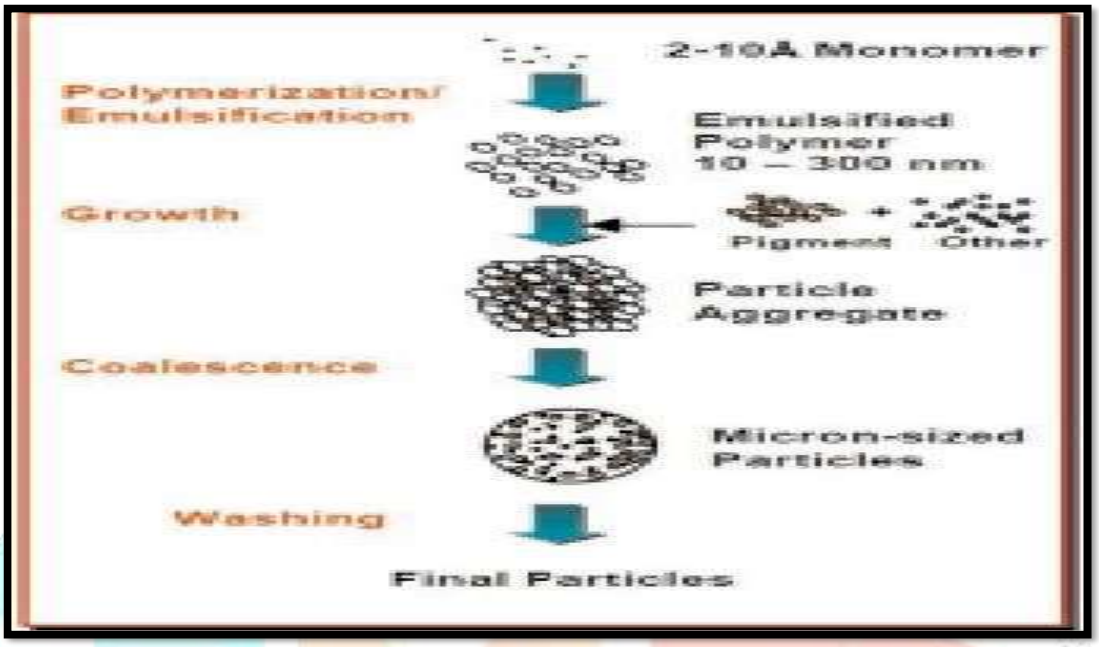


**Figure No:7 multiple emulsion method.**

### 4. Reverse-Phase Evaporation:

Reverse-phase evaporation. The reverse-phase evaporation technique is a widely utilized method for liposome preparation. In this process, lipids are initially dissolved in an organic solvent, which is subsequently brought into contact with an aqueous phase containing the target substance for encapsulation. The system's phase behavior varies depending on the organic solvent's miscibility with water: it forms a singlephase system when using water-miscible solvents (e.g., ethanol) or a twophase system when employing water-immiscible solvents (e.g., diethyl ether). In single-phase systems, phospholipid molecules disperse uniformly in the aqueous medium, while in biphasic systems, these molecules spontaneously arrange into a monolayer at the organic-aqueous interface. The liposome formation process involves several sequential steps: first, water-in-oil (W/O) microemulsions are generated through ultrasonic treatment; second, organic solvents are eliminated using a rotary evaporator; and finally, phospholipid molecules reorganize into vesicular structures in aqueous medium. The resulting suspension is then passed through a polycarbonate filter membrane, yielding uniform monolamellar liposomes with controlled size distribution. This versatile method is universally applicable to various lipids, lipid mixtures, and small molecules, demonstrating exceptional capabilities in encapsulating genes, organic solventresistant drugs, and water-soluble compounds. However, a notable limitation lies in the temperature requirements during the preparation process, particularly during ultrasonication and organic solvent evaporation under reduced pressure, which may potentially denature heat-sensitive substances.

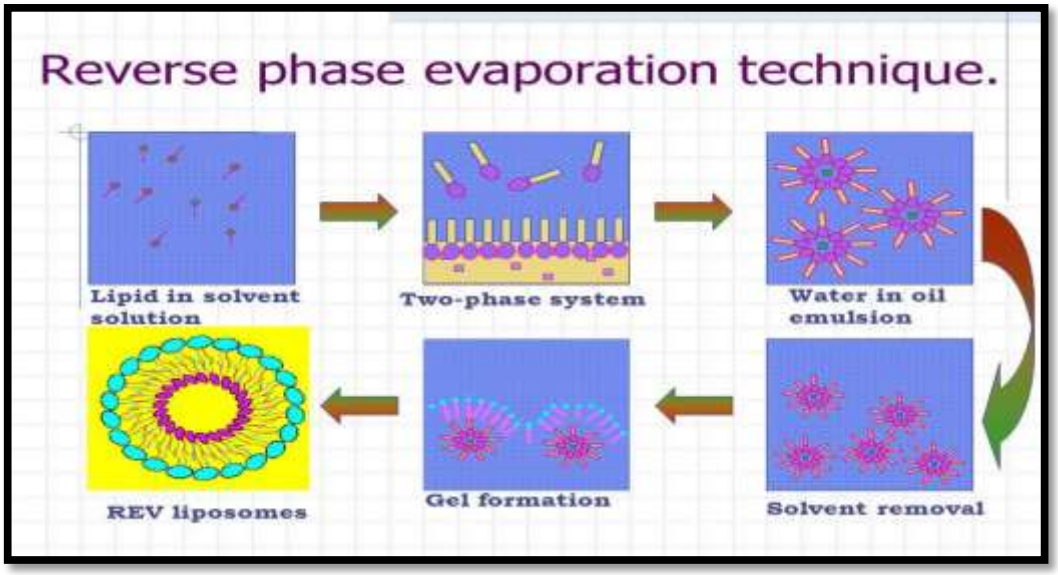


**Figure No:8 reverse phase evaporation.**

**5. Gradient Method:**

The gradient method leverages the concentration or chemical nature differential between the interior and exterior of liposomes to facilitate drug encapsulation. Notably, this approach encompasses three established techniques: the pH gradient method, acetate gradient method and ammonium sulfate gradient method. Among these, the pH gradient method involves preparing an internal buffer solution containing specific acidic components (e.g., citrate and tartaric acid), followed by adjusting the external pH of liposomes using techniques such as dialysis or column chromatography to approximate physiological pH, thereby establishing a pH gradient across the liposomal membrane. Under controlled temperature conditions, the target drug is mixed with pre-formed blank liposomes possessing the established gradient. In this system, the drug exists in a lipophilic neutral form in an external neutral pH environment, enabling its passive diffusion across the lipid bilayer. Once inside the liposome aqueous phase, the drug undergoes protonation, converting to an ionic form that is effectively trapped within the liposomal core. This innovative process achieves efficient drug encapsulation. Furthermore, both the ammonium sulfate gradient method and the calcium acetate gradient method operate on analogous principles for liposome preparation. demonstrated that the encapsulation efficiency of liposomal diclofenac approached 100% when employing a calcium acetate gradient, while the pH gradient method yielded a 5–50% encapsulation efficiency for FITC-insulin liposomes. This suggests that weakly acidic drugs can be effectively loaded into liposomes via an acetate gradient, while the pH gradient method is particularly suitable for liposomal peptide preparation. The nucleotide analogue dimeric aminobenzimidazole, a STING agonist,faces the challenges of low serum stability and poor cell membrane permeability. To address these issues, Zhang et al. successfully encapsulated dimeric aminobenzimidazole in liposomes using the ammonium sulfate gradient method, achieving a particle size below 150 nm. This reduced particle size minimizes rapid clearance by the reticuloendothelial system, thereby extending its circulatory time in the bloodstream. Furthermore, the lower surface charge of these liposomes decreases nonspecific binding to plasma proteins, enhancing both circulation duration and cellular permeability.

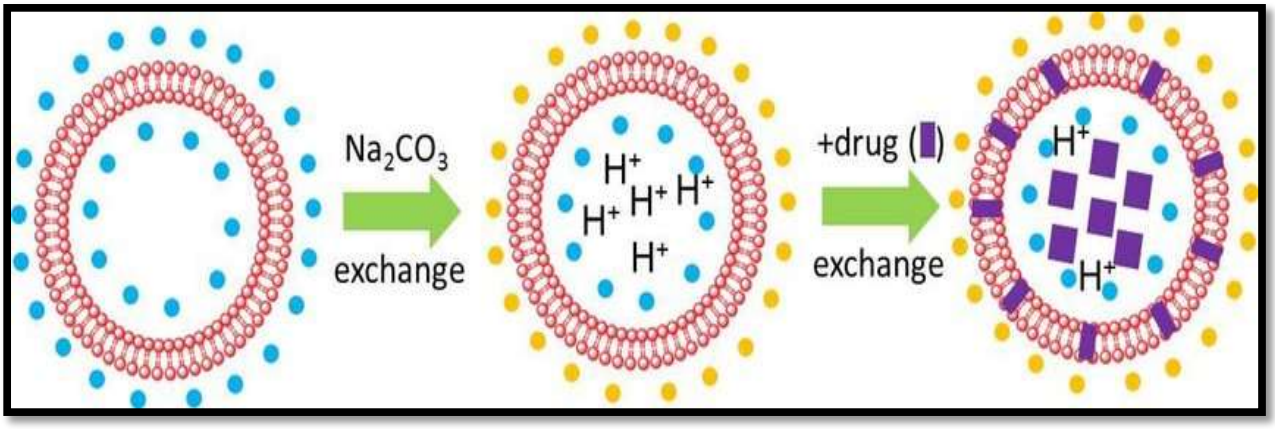


**Figure No:9 gradient method**

## 6. Microfluidic Technology:

Microfluidic chips represent innovative instrumentation platforms widely used in synthetic chemistry and biology, commonly referred to as microfluidic reaction systems. This technology enables material synthesis by precisely controlling the flow of minute liquid volumes through micron-sized channels. By utilizing microfluidic devices, high pressures are converted into intense shear forces, facilitating the preparation of liposomes without the need for ultrasound or toxic chemicals. Furthermore, this technology offers precise control over reaction conditions. When the Reynolds number within the microchannel is significantly below 1, the fluid flow is predominantly laminar, with inertial forces dominating. Under such conditions, fluid mixing primarily relies on the passive diffusion of molecules, resulting in the rapid and efficient transfer of materials and heat. However, surfactants are often required to ensure smooth fluid flow and maintain stability, which may increase the risk of product contamination. Guet al. successfully synthesized baicalin-loaded liposomes using a microfluidic technique, achieving an exceptional encapsulation efficiency of 95.323  0.481% and a uniform particle size distribution of 62.320.42 nm. Compared to the free baicalin monomer, the fluorescence intensity of BCL-LPs in the zebrafish liver region gradually decreased as the concentration of baicalin increased. This observation indicates a significant suppression in the expression of the proto-oncogene krasv12, further demonstrating the enhanced anti-tumor efficacy of baicalin-loaded liposomes in the zebrafish model[12,13]

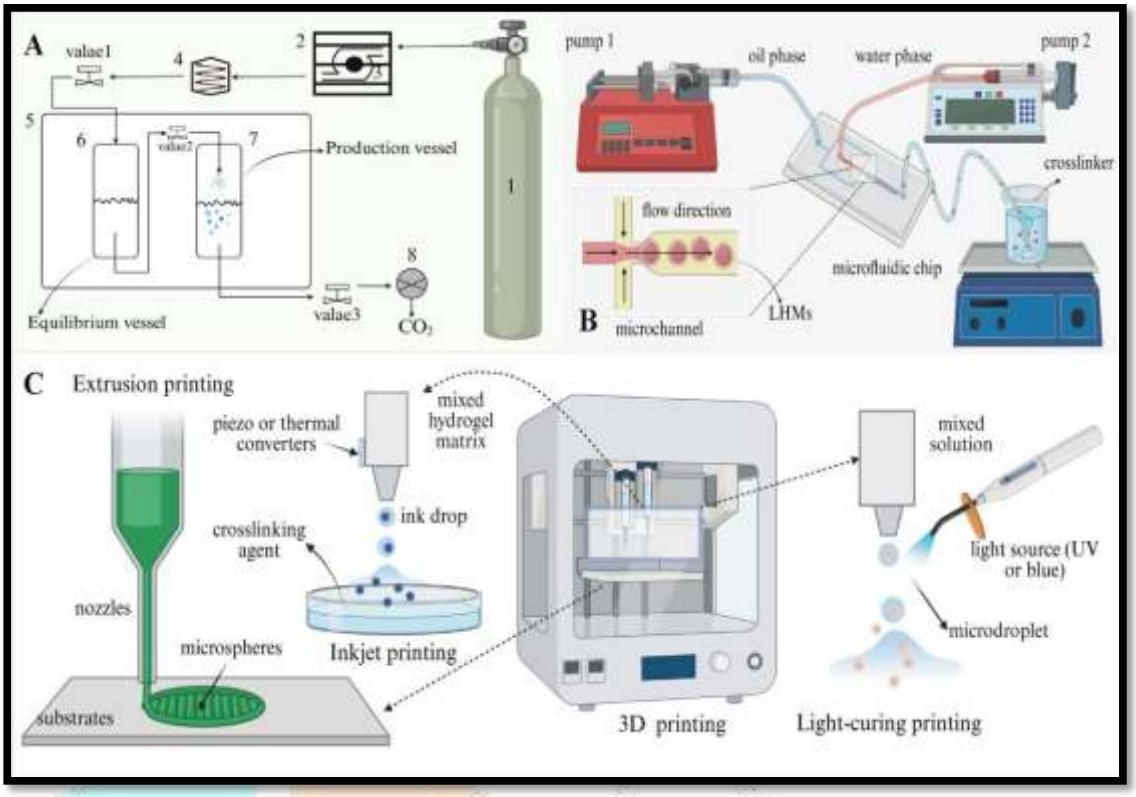


**Figure No:10 construction of liposomes and LHMS.**

## Characterization of Hydrogels:

This section delves into the crucial properties of hydrogels, such as mesh size, swelling behavior Porosity, microstructure, mechanical strength, and degradability. We start by examining why These characteristics are vital for the effectiveness of hydrogel-based drug delivery systems. Next, we investigate the common techniques used to measure these physical properties. We then highlight how the manipulation of these properties can enhance hydrogel performance. The characterization techniques are neatly summarized in Recently, Denze retal. have offered an extensive overview of the methods employed in hydrogel characterization.

**Table 1. Comparison of common methods used in hydrogel characterization.**

| Property | Methods | Advantages | Disadvantages |
|---|---|---|---|
| **Mesh size** | Rheological testing | Non-destructive, suitable for varied hydrogels, time-dependence analysis. | Specialized equipment needed, complex interpretation. |
| | Estimation from swelling ratio | Straightforward, informative. | Limited by the drawbacks of swelling ratio methods. |
| | Mechanical testing | Correlates with mechanical properties, diverse application. | Indirect estimation, sample preparation can be complex. |
| | Scattering techniques | Broad applicability, non-destructive, in-situ analysis possible. | Advanced equipment required, sensitive to sample preparation. |
| **Swelling ratio** | Weight change Volumetric change | Simple, cost-effective, broadly applicable. | Influenced by environmental factors, not for fast-swelling gels. |

| | | | |
|---|---|---|---|
| | | Direct measurement, effective for significant swelling. | Challenging for irregular shapes or small samples. |
| | Differential scanning calorimetry (DSC) | Quantitative, non-destructive. | Specialist interpretation needed, higher equipment cost. |
| | Estimation from swelling ratio | Straightforward, informative. | Limited by the drawbacks of swelling ratio methods. |
| | Mercury intrusion porosimetry | Accurate pore size and distribution, reproducible. | May alter structure, mercury is hazardous. |
| | SEM | Detailed surface imagery, pore size and distribution. | Dry samples only, surface-level. |
| **Property** | **Methods** | **Advantages** | **Disadvantages** |
| **Porosity** | Gas adsorption | Non-destructive, good for surface area and microporosity. | Limited to surface, not suitable for all types. |
| | Capillary flow porometry | Provides thorough porosity data. | Requires careful choice of phases. |
| **Microstructure** | SEM | Detailed surface imagery, pore size and distribution. | Dry samples only, surface-level. |
| | TEM | High-resolution internal images. | Requires meticulous preparation, small coverage. |
| | NMR | Molecular insights, non-destructive. | Expensive, complex data interpretation. |
| | AFM | Nanoscale surface topology. | Surface-specific, complex sample prep. |
| | Confocal microscopy | 3D imaging, non-destructive. | Limited penetration, fluorescence needed. |
| | X-ray CT | Non-destructive 3D internal imaging, high resolution. | High cost, requires contrast agents for some hydrogels. |
| **Mechanical strength** | Dynamic Mechanical Analysis (DMA) | Frequency-dependent properties. | Requires specific equipment and sample shapes. |
| | Rheological testing | Measures viscoelastic properties, non-destructive. | Complex interpretation, condition-sensitive. |
| | Tensile and compression testing | Direct strength and elasticity measurement. | Destructive, specific sample shapes necessary. |
| **Degradability** | Mass loss measurement | Direct, simple quantification. | May overlook subtle changes. |
| | Gel Permeation Chromatography | Detailed profile, molecular weight | Complex, requires solubilization. |

| | | | |
|---|---|---|---|
| | (GPC) | insight. | |
| | NMR | Degradation pathways at the molecular level. | Requires expensive equipment, expertise for data interpretation. |
| | Viscosity measurement | Indicates molecular weight changes. | Indirect, requires careful interpretation. |

**1. Mesh Size and swelling Behavior:**

The swelling behavior of hydrogels in drug delivery significantly impacts drug release and diffusion, making it a crucial factor in their application. Hydrogels, with their crosslinked polymer networks, facilitate the movement of liquids and solutes through open spaces or meshes. The mesh size ($\xi$) of hydrogel used in drug delivery, typically less than 200 nm, is pivotal indetermining the interaction between the drug and the polymer network, thereby controlling the diffusion of drugs. However, it is important to note that hydrogels often display a wide range of mesh sizes due to network heterogeneity and polymer polydispersity. This variability is especially pronounced in hydrogels formed through free-radical polymerization.

**2. Porosity and Microstructures:**

Porosity ($P$) and microstructure are foundational to the biomedical utility of hydrogels, as they dictate the internal void spaces and structural arrangement. These properties are crucial for fluid dynamics, including drug delivery and nutrient-waste exchange in tissue engineering contexts, and are influenced by polymerization techniques and cross-linking density. The microstructure, encompassing pore size, shape, and distribution, is shaped by synthesis conditions and affects the mechanical properties, biocompatibility, and biodegradability of hydrogels. Optimizing porosity and microstructure is therefore vital for designing hydrogels that mimic the extracellular matrix, promoting cell growth and migration, enabling precise drug release, and ensuring predictable degradation for seamless tissue integration. The creation of interconnected porosity within polymeric hydrogels represents a significant innovation, improving performance through enhanced solvent transport via convective flow rather than simple diffusion.This feature is especially critical in the biomedical application of hydrogel, where tailored porosity and pore size distribution facilitate drug release. Various fabrication methods, including foaming, phase separation, in situ crosslinking polymerization, particulate leaching, freeze-drying, and reverse casting, have been employed to achieve hydrogels with precise porosity, significantly impacting their porosity and microstructure. Research indicates that the swelling and degradation behaviors of hydrogel are profoundly influenced by its porous characteristics, such as void fraction and pore interconnectivity. Moreover, the drug delivery efficacy of hydrogel is largely determined by its water content and porosity, which affect solute absorption and diffusion. Advanced production techniques, like solvent casting, electrospinning, fused deposition modeling, and 3D printing, have been investigated for crafting porous scaffolds, underscoring the necessity for innovative approaches in hydrogel development to optimize their porosity and microstructure for biomedical applications.

The common method used in the calculation of the porosity of the hydrogel is based on the weight of the hydrogel before and after drying. incorporating the previously mentioned swelling ratio as follows:

$$P = \frac{Ws-wd)/\rho\omega}{Wd/\rho p+(Ws-Wd)/\rho\omega} = \frac{Q/\rho\omega}{1/\rho p+Q/\rho\omega} \quad (1)$$

where $\rho_p$ is density of water and $\rho_w$ is density of polymer. This approach to assessing porosity is more straightforward than alternative techniques, which include the diffusion of probes within the hydrogel, measuring water content through differential scanning calorimetry (DSC), and testing the permeation of probe solutes. Other complex methods such as mercury porosimetry, gas pycnometry and liquid extrusion porosimetry also fall into this category. The microstructure of hydrogels is typically characterized using a

variety of microscopy techniques, including optical microscopy, scanning electron microscopy transmission electron microscopy (TEM) and atomic force microscopy (AFM) which elucidate surface morphology and topographical details. For a more in-depth internal analysis, micro-computed tomography (Micro-CT), or X-ray microtomography, serves as a high-resolution, nondestructive method to evaluate pore size, distribution, and the directional orientation of pores, providing a comprehensive view of the internal structure.

**3. Mechanical Properties:**

The mechanical properties of hydrogels, such as tensile strength, elasticity, and viscoelasticity, play a pivotal role in their application for drug delivery, enabling them to mimic the mechanical environment of natural tissues, support cellular functions, and withstand dynamic physiological stresses. These properties are essential for the successful integration of hydrogels into biological systems, facilitating sustained and controlled drug release. Mechanical deformation of hydrogels, through methods like mechanical force, ultrasound, and magnetic fields, offers a strategic avenue for drug release This approach can alter the network structure, increase mesh size, and induce convective flow within the hydrogel, enabling pulsatile release patterns that can mimic biological signaling processes, such as the release of insulin postprandially.To accurately assess the mechanical properties of hydrogels, researchers utilize rheological measurements and uniaxial compression tests. Micro-rheology and mechanophores, used to probe the local mechanical properties within the heterogeneous hydrogel environment, also fall into this category. Rheological measurements, involving deformation and frequency sweep tests, determine the viscoelastic properties of the hydrogel. This process includes estimating the linear viscoelastic region and subsequently determining the elastic ($G'$) and viscous ($G''$) moduli. From these values, the aforementioned effective cross-link density can be calculated. Complementary to this, uniaxial compression tests measure the hydrogel's response to force, providing data on stress, strain, and the compression modulus ($G$). Compared to uniaxial tensile mechanical tests, rheological tests require much less preparation of samples, especially for extremely soft gels. However, preparing uniformly sized samples for mechanical testing can be very challenging and varies significantly from one researcher to another, leading to less consistent reproducibility in experiments.

However, challenges such as the highwater content and network heterogeneity of hydrogels often compromise their mechanical stability, posing limitations to their practical utility. To address these issues, research has been directed towards enhancing the mechanical performance of hydrogels through innovative strategies, including the development of double-network hydrogels and the introduction of chemically or ionically cross-linked hydrogels. Noteworthy is the work by which introduced "sacrificial weak bonds" in double network hydrogels to improve mechanical durability. This approach combines a densely cross-linked polyelectrolyte network with a loosely cross-linked polyacrylamide network. The sacrificial breakdown of the former absorbs energy and prevents crack propagation, significantly boosting the toughness of hydrogels.Advancements continue with the exploration of reversible physical interactions such as ionic bonds, crystallization, hydrophobic interactions, and hydrogen bonding—to further enhance the resilience of hydrogel networks. A significant breakthrough by Suo et al. involved creating a dual cross-linked double network hydrogel through a one-pot process incorporating sodium alginate and acrylamide with NN'-methylenebisacrylamide and calcium ions. This innovation leads to a hydrogel that, after photoinitiated polymerization, showcases remarkable extensibility and toughness, is able to stretch more than 20 times its original length, and achieves a tear energy of nearly 9000 J/m$^2$. Its notable stretchability, even in the presence of notches allowing for a 17-fold extension from its original length, exemplifies the potential of integrating physical interactions to significantly bolster the mechanical properties of hydrogels for drug delivery and other biomedical applications.

**4. Degradability:**

Degradability in hydrogels is a key attribute tailored for biomedical applications, allowing these materials to break down into biocompatible by-products that can be safely metabolized or excreted by the human body This property ensures that hydrogelbased devices, such as drug delivery systems, tissue engineering scaffolds, or temporary implants, perform their intended therapeutic functions and then degrade at a controlled rate to minimize long-term adverse effects. The degradability rate and mechanism—often achieved through hydrolysis or enzymatic degradation—are influenced by the chemical composition of hydrogel, including the nature of the polymeric backbone and the presence of degradable linkages. For example, hydrogels incorporating poly (lactic-co-glycolic acid) or peptides designed to be cleaved by specific enzymes can provide precise control over degradation timescales, aligning with tissue healing

processes or drug release profiles Optimizing degradability for biomedical hydrogels is crucial for their successful integration and function in medical treatments, promoting efficient treatment while avoiding the need for surgical removal.[14,15,16,]

**Factor Affecting Liposome:**

**1] Lipid composition:** Phospholipids cholesterol Ratio this Ratio is crucial for controlling Liposome size stability, drug loading and drug release properties. Cholesterol for example Rigidity And stability to the membrane

**2] Phospholipids properties**: The features of the phospholipid itself, such as acyl chain length degree of saturation and polar head group influence the lipid phase transitions temperature and stability.

**3] Phase transition temperature (TC):** the temperature at which the lipid bilayer transition Form a liquid to a gel like state significantly affect the membrane fluidity influencing drug encapsulation efficiency and leakage

**4] Partical characteristics:** Partical size: Liposome size directlyimpact their_distribution in biological systems such with different size leading varying level of uptake by organ like the liver and spleen.

**Environmental And External Factor:**

**1] Temperature:** High temperature can cause Liposome to lose stability and potentially lead to aggregation while freeze-thawing can Also affect their structure and stability.

**2] Light Exposure:** Liposome can be sensitive to light particularly Uv- Radiation which can impact their photostability over time.

**3] PH And Osmotic Gradient**: changes in PH And the presence of Osmotic Gradient can influence the stability and integrity of the liposomal membrane.
**4] Stimull Responsive Factor:** Liposome can be designed to Respond to specific stimuli such as PH, light or enzyme to trigger drug Release At the target site.

**5] Surface Modification:** Targeting ligand attaching molecule like Antibodies or peptides to the liposome surface enable targetting the specific cell or tissue enhancing delivery efficiency and potentially improving stability by preventing nonspecific interaction.

**Application:**

**1] Controlled And sustained Drug Release:**

- Liposome inside Hydrogel microsphere Act as Reservoirs enabling multiRelease control (form Liposome -hydrogel -tissue)
- Useful in long term therapies Such as chronic pain Management or cancer treatment where steady drug level Are need.

**2] Targeted Cancer Therapy:**

- Microspheres Can be Engineered to localize in tumor tissue.
- Liposome carry chemotherapeutic drug eg (Doxorubicin,Paclitaxel).
- Hydrogel provide sustained Release Reducing systemic toxicity.

**3] Protein Peptide and Nucleic acid:**

- Sensitive Biomolecules (growth factor SiRNA, mRNA, CRISPR component are protected with in Liposome form enzymatic degradation.
- Hydrogel ensure gradual Release And localized effect Useful gene therapy and regenerative medicine.

**4] Tissue Engineering and Regenerative medicine:**

- Composite microspheres can deliver Growth factor like VEGF or BMPS in a controlled way.
- Enhance wound Healing, Bone cartilage Regeneration and Angiogenesis.

**5] Vaccine And immunotherapy:**

- Liposome Are carries for Antigen /Adjuvant.
- Hydrogel Act As depot system prolonging immune Stimulation.
- Potential in cancer vaccine and infectious disease prevention.

**6] Transdermal And Mucosal delivery:**

- Microspheres Can be designed for nasal ocular or oral Route.

Example -liposome -hydrogel composites used ocular drug delivery for Glucoma to Extend dosing intervals.

**Conclusions:**

Hydrogels have revolutionized the feld of drug delivery, offering versatile and sophis- Ticated platforms for targeted therapy and regenerative medicine. Despite their promising Attributes, such as highwater content, biocompatibility, and controlled release capabilities, the path toward their clinical adoption is fraught with regulatory, manufacturing, and biological challenges. To bridge the gap between laboratory research and clinical application future endeavors should focus on simplifying hydrogel designs to meet regulatory Standards, developing improved theoretical models for predictable therapeutic outcomes, and exploring new material combinations to enhance biocompatibility. Embracing these Strategies will propel the advancement of hydrogel technologies, paving the way for their Integration into precision medicine and opening new avenues for customized and effective Healthcare solutions.

**REFERECE:**

**[1]** Grijalvo, S., Mayr, J., Eritja, R., & Díaz, D. D. (2016). Biodegradable liposome-encapsulated hydrogels for biomedical applications: A marriage of convenience. *Biomaterials science*, *4*(4), 555-574.

**[2]** Chronopoulou, L., Falasca, F., Di Fonzo, F., Turriziani, O., &Palocci, C. (2022). siRNA transfection mediated by chitosan microparticles for the treatment of HIV-1 infection of human cell lines. Materials, 15(15), 5340.

**[3]** Liu, P., Chen, G., & Zhang, J. (2022). A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. *Molecules*, *27*(4), 1372.

**[4]** Ferraris, C., Rimicci, C., Garelli, S., Ugazio, E., & Battaglia, L. (2021). *Nanosystems in Cosmetic Products: A Brief Overview of functional, market, regulatory and safety concerns. Pharmaceutics 2021, 13, 1408*.

**[5]** Yadwade, R., Gharpure, S., & Ankamwar, B. (2021). Nanotechnology in cosmetics pros and cons. *Nano Express*, *2*(2), 022003.

**[6]** Kimura, M., Fukumoto, K., Watanabe, J., Takai, M., & Ishihara, K. (2005). Spontaneously forming hydrogel from water-soluble random-and block-type phospholipid polymers. *Biomaterials*, *26*(34), 6853-6862.

**[7]** You, Y., Yang, J., Zheng, Q., Wu, N., Lv, Z., & Jiang, Z. (2020). Ultra-stretchable hydrogels with hierarchical hydrogen bonds. *Scientific Reports*, *10*(1), 11727.

**[8]** Liang, H. C., Chang, W. H., Liang, H. F., Lee, M. H., & Sung, H. W. (2004). Crosslinking structures of gelatin hydrogels crosslinked with genipin or a water-soluble carbodiimide. *Journal of applied polymer science*, *91*(6), 4017-4026.

**[9]** Zhu, R., Yin, Z., Liu, N., Wang, Z., Zhang, H., Li, J., ... & Zheng, A. (2023). Polymyxin B-Modified fosfomycin liposomes target gram-negative bacteria and exert synergistic antibacterial effect. *ACS omega*, *8*(48), 45914-45923.

**[10]** Jang, Y. J., Kang, S. J., Park, H. S., Lee, D. H., Kim, J. H., Kim, J. E., ... & Bhang, S. H. (2025). Drug delivery strategies with lipid-based nanoparticles for Alzheimer's disease treatment. *Journal of nanobiotechnology*, *23*(1), 99.

**[11]** Zhang, M., Xiang, C., Niu, R., He, X., Luo, W., Liu, W., & Gu, R. (2025). Liposomes as versatile agents for the management of traumatic and nontraumatic central nervous system disorders: drug stability, targeting efficiency, and safety. *Neural Regeneration Research*, *20*(7), 1883-1899.

**[12]** Wang, X., Liu, J., Wang, P., DeMello, A., Feng, L., Zhu, X., ... & Gong, X. (2018). Synthesis of biomaterials utilizing microfluidic technology. *Genes*, *9*(6), 283.

**[13]** Gu, Y., Jin, L., Wang, L., Ma, X., Tian, M., Sohail, A., ... & Wang, D. (2024). Preparation of baicalin liposomes using microfluidic technology and evaluation of their antitumor activity by a zebrafish Model. *ACS omega*, *9*(40), 41289-41300.

**[14]** an, Z., Wang, P., Mao, G., Yin, T., Zhong, D., Yiming, B., ... & Yang, W. (2020). Dual pH-responsive hydrogel actuator for lipophilic drug delivery. *ACS applied materials & interfaces*, *12*(10), 12010-12017.

**[15]** Jia, D., & Muthukumar, M. (2018). Topologically frustrated dynamics of crowded charged macromolecules in charged hydrogels. *Nature Communications*, *9*(1), 2248.

**[16]** Chen, K., Li, S. F., & Muthukumar, M. (2022). Boundaries of the topologically frustrated dynamical state in polymer dynamics. *ACS Macro Letters*, *11*(5), 699-705.

**[17]** C. Patel, G., & A. Dalwadi, C. (2013). Recent patents on stimuli responsive hydrogel drug delivery system. *Recent Patents on Drug Delivery & Formulation*, *7*(3), 206-215.

**[18]** Food and Drug Administration. (2016). FDA Executive Summary. Classification of Wound Dressings Combined with Drugs. *FDA: Silver Spring, MD, USA*.