A Comprehensive Review on Glycerosomes: Innovative Nanovesicles for Effective Therapeutic Delivery

Ms. Kanika[1], Prof. (Dr.) Naresh Singh Gill[2], Ms. Neelam Sharma[3], Ms. Amandeep Kaur[4], Ms. Supneet Kaur[5]

[1]Assistant Professor at Lamrin Tech Skills University (LTSU), Punjab
[2] Executive Dean/ Director at Lamrin Tech Skills University (LTSU), Punjab
[3] Department of Pharmaceutics at Lamrin Tech Skills University (LTSU), Punjab
[4]Associate Professor at Lamrin Tech Skills University (LTSU), Punjab
[5]Associate Professor at Lamrin Tech Skills University (LTSU), Punjab
[1]Kanikapharma1993@gmail.com, [2]rip.director@rgi.ac.in, [3]neelamsharma3690@gmail.com, [4]ranaji.kaur@gmail.com [5]supneetanterkaur@gmail.com

Abstract

Glycerosomes are new vesicular drug delivery systems for both topical and systemic drug delivery. These non-invasive carriers have the ability to penetrate deeper into the skin than a free drug. Glycerosomes consist of phospholipids, water, and a high amount of glycerol (from 20 to 40%), all nontoxic and well-tolerated elements used for topical formulations. When the concentration of glycerol is high, it enhances the drug's penetration by increasing the flexibility of the vesicles. This also improves the stability of the vesicles, ensuring their stability throughout. They are capable of enclosing both lipophilic and hydrophilic drugs and shielding them from deterioration. Glycerosomal carriers are nowadays the most interesting area of work for researchers. This review article provides an overview of the structure, benefits, composition, methods for preparations, characterization, and applications of glycerosomes.

Keywords: *Glycerosomes, Glycerol, Penetration, Drug Delivery.*

1. INTRODUCTION

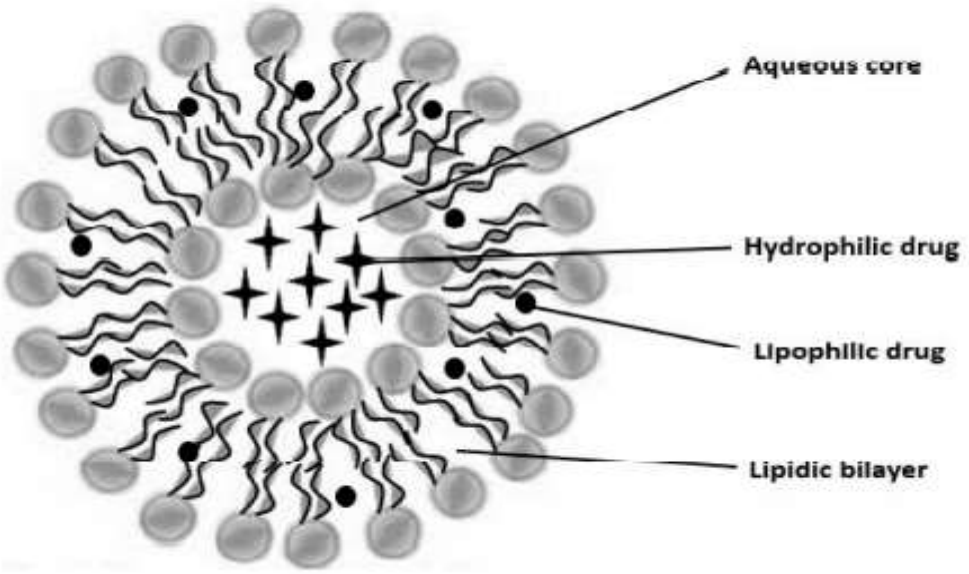
Glycerosomes represent a new class of nanovesicles that can substantially improve bioactive compounds therapeutic delivery. [1] The key feature of these vesicles is their introduction of glycerol into the phospholipid bilayer, which imparts a distinct set of physicochemical properties relative to traditional liposomes. [2] Using glycerol in lipid vesicles improves their flexibility, stability, and the encapsulation of hydrophilic and hydrophobic molecules. In this review, we provide an extensive discussion based on the design, properties, applications, and perspectives of glycerosomes for drug delivery systems. [3]

Researchers have investigated several nanocarriers, such as liposomes, Niosomes, and ethosomes, to ascertain effective medication delivery methods. [4] Glycerosomes have emerged as a potential invention owing to their distinctive structural and functional characteristics. The integration of glycerol into the phospholipid bilayer enhances its flexibility and prolongs its

durability. [3] Glycerosomes are optimal for the delivery of both hydrophilic and hydrophobic pharmaceuticals. This review encapsulates the prevailing research on the endocrine system. The encapsulated vesicular system is essential in cosmetic formulations. specifically, glycerosomes derived from natural plant bio actives and synthetic substances. [5] This review focuses on various techniques of preparation, characterisation, and documented investigations.[6]

1.1 VESICULAR DRUG DELIVERY SYSTEM

Vesicles are tiny particles that carry other particles around. They are made up of one or more lipid bilayers that are surrounded by water and some chemicals that mix with water, such as surfactants or phospholipids. [7] Vesicles can sequester lipophilic or hydrophilic drugs within the lipid bilayer or the aqueous compartment. [8] They may reduce the risk of medication toxicity by targeting drug delivery to the specific site of action and decreasing concentrations in other areas of the body. [9] Entrapment in vesicles prolongs the lifetime of medications in systemic circulation. [10] Also, it showed that the lipid parts of vesicular systems can get into the stratum corneum and change the intercellular lipid matrix. This makes it easier for antifungal agents to get into the stratum corneum. [11] Even though liposomes and niosomes have been around for a while, they aren't used or effective very often because they aren't very stable. For example, drugs can clump together, leak out, or fuse together. [12]



General Structure of Vesicular System (Adapted from Ref. No.64)

1.2 COMPOSITION AND STRUCTURE OF GLYCEROSOMES

Glycerosomes, a novel drug delivery vehicle based on vesicle technology, consist of cholesterol and phospholipids. They are analogous to conventional lipid-based vesicular

systems. The thin film's phospholipid component rapidly self-assembles into bilayer vesicles upon the introduction of water. Furthermore, at concentrations of 10, 20, 30, 40, and 50% v/v, glycerol, land, and water comprise the most significant features. Currently, experts recommend topical and cutaneous administration of the drug moiety using glycerosomes. Topically administering the drug moiety is a non-toxic and completely risk-free method. [13-16]

1.2.1 STRUCUTRE OF GLYCEROL

The three hydrophilic groups that give glycerol its hydrophilic nature is found in this viscous, alcohol-based liquid. Glycerol is often found in both vegetable and animal fats since it is a triglyceride. Most frequently, it is obtained via producing soap or as a by-product of producing biodiesel.

1.2.2 PHOSPOHLIPIDS

Glycerosomes, like other vesicular systems, can grow by using phospholipid from both natural and artificial sources. The head, tail, and related alcohol group composition of the phospholipid can be used to classify it into several groups. These are compatible with almost all components in addition to being amphiphilic. When water is introduced to the thin layer of phospholipid, it can assemble into a multitude of shapes. The way that phospholipids self-assemble in hydration media is dependent on certain phospholipid properties. There are numerous types of phospholipids, distinguished by differences in their backbone architectures and the alcohol moiety they contain. [17]

1.2.2.1 TYPES OF PHOSPHOLIPIDS

Glycerophospholipids:

Glycerophospholipids are derived from eukaryotic organisms. Glycerol is the primary component of these lipids. The hydrophilic head group of these lipids changes to form heartlipin, phosphatidylcholine, phosphatidylserine, and other lipids. These lipids change their acyl chains to produce dipalmitoyl phosphatidylcholine and dimyristoyl phosphatidylcholine.[18]

Sphingomyelins:

These phospholipids, which come from animal cell walls, are distinct from glycerophospholipids in that they have a sphingosine backbone instead of a glycerol one. These phospholipids differ not only in their chemical structures but also in the number of groups present in their acyl chains. We regard glycerophospholipids as symmetric, and sphingophospholipids as asymmetric. While paraffin residues have fewer acyl groups than natural sphingomyelins, naturally occurring sphingomyelins have more than 20. This leads to the term asymmetric. Phosphatidylcholine, an example of a glycerophospholipid, has an identical chain length, making them symmetric molecules.[18]

1.23 CHOLESTROL

The bulk of animal cell membranes are made of cholesterol. Many features of the membrane are recognized to be impacted by it. The fluidity, stability, thickness, and rigidity of cell membranes are all influenced by cholesterol. Glycerosome stability is increased by the addition of cholesterol. Cholesterol predominantly interacts with the liposomes' interior cavity because of its hydrophobic nature, which keeps it stable. [19]

1.3 NATURE OF DRUG ENCAPSULATED

Glycerosomes and liposomes can contain both hydrophilic and hydrophobic drug moieties incorporated in them. Phospholipid and cholesterol are used to make the poorly water-soluble drugs that are embedded in the vesicles' outer covering, while the hydrophilic drug is placed in the vesicles' core. Thin film hydration is a commonly used method for encapsulating hydrophilic compounds. This method decreases the effectiveness of the drug moiety's encapsulation even while it helps the water-loving drug moiety's encapsulation. These vesicular networks deliver the drug to the intended site without letting it deteriorate. [20]

1.4 POTENTIAL FEATURES OF GLYCEROSOMES

1. They are fully biocompatible and biodegradable.
2. They are compatible with most of the drugs.
3. They protect the encapsulated drug from metabolic degradation.
4. They can penetrate into deeper layers of skin, so most suitable for topical drug delivery
5. They contain glycerol, which act as edge activator for phospholipid bilayer when used in concentration above than 10 percent.
6. They consist of hydrophobic and hydrophilic moieties together and can able to entrap drug molecules with wide range of solubility.

2. ADVANTAGES OF GLYCEROSOMES

Glycerosomes are a novel drug delivery system that combines the benefits of liposomes and glycerol to enhance the topical delivery of active pharmaceuticals ingredients (APIs). Here are some advantages of glycerosomes:

1. Enhanced Drug Solubility: - Glycerosomes enhance the solubility of weakly water-soluble drugs by incorporating glycerol, which serves as a co-solvent.[21]

2. Controlled Drug Release: - Glycerosomes allow controlled and long-lasting release of the drugs they hold, which could improve therapeutic effectiveness and lower the number of times a person needs to take a dose.[22]

3. Potential for Targeted Delivery: - The incorporation of ligands or other surface modifications can design glycerosomes for targeted drug delivery, just like other vesicular systems.[23]

4. Enhanced Skin Penetration: -

1. Glycerol functions as a humectant, enhancing skin moisture and softening the stratum corneum. This enhances the absorption of active substances via the skin.

2. Glycerosomes have enhanced efficacy in delivering drugs and other bioactive compounds into and through the skin compared to conventional liposomes.

5. Improved Skin Permeability: - Glycerol in glycerosomes enhances the hydration of the stratum corneum, hence enhancing drug permeation through the skin, which renders them very efficacious for topical and transdermal drug administration.[24]

6. Thermal and Osmotic Protection: - Glycerosomes have greater resistance to osmotic stress and temperature fluctuations than traditional liposomes, making them appropriate for storage and transport under various circumstances.[24]

7. **Reduced Dehydration Risk: -** Glycerol inhibits vesicle dehydration, thereby preserving their effectiveness over prolonged durations, especially under adverse environmental circumstances.

8. **Biocompatibility: -**

- Glycerol is a naturally occurring, non-toxic, and biocompatible substance, making glycerosomes safe for use in medical and cosmetic applications.
- The vesicles are well-tolerated by the skin and other tissues, minimizing the risk of irritation or adverse reactions.[25]

9. Versatility: - Glycerosomes can encapsulate both hydrophilic and hydrophobic drugs, offering flexibility in delivering a wide range of therapeutic agents.[2] Glycerosomes are suitable for multiple delivery routes, including:

- **Topical**: For skin treatments and hydration.
- **Transdermal**: For systemic drug delivery via the skin.
- **Ocular**: For treating eye-related conditions.
- **Oral**: For improved drug absorption in the gastrointestinal tract.

10. Improved Patient Compliance: - Glycerosomes enhance drug stability, enable controlled release, and increase skin permeability, thereby facilitating drug administration and improving patient compliance, particularly in transdermal systems or pain treatment.[26]

11. Stability Improvement: - The incorporation of glycerol fortifies the lipid bilayer structure of the vesicles, thereby enhancing the physical and chemical stability of the drug delivery system.[27]

12. Enhanced Drug Loading Capacity: - The incorporation of glycerol may enhance the encapsulation efficiency of certain drugs by reducing the rigidity of the bilayer membrane.[6]

3. METHODS FOR PREPARATION OF GLYCEROSOMES: - The glycerosomes can be prepared by different approaches used for the preparation of liposomes.

The preparation of glycerosomes are based on following three strategies: -

a) Mechanical methods
b) Organic solvent replacement methods
c) Size transformation methods

A) MECHANICAL METHODS:

i. Lipid thin film hydration:

The glycerosome-making process described by Bangham et al. is the most straightforward.[5] We create the thin film by dissolving the phospholipid in an organic solvent and letting it dry. Next, we introduce an aqueous phase to the thin film, a solution of water and glycerol, and sonicate the resulting dispersion with a high-intensity ultrasonic sonicator. This process offers the benefit of producing a formulation with superior physical properties, such as a spherical shape and smooth texture, along with enhanced encapsulation efficiency when compared to alternative methods.[28][29][30-33] We use an aqueous hydration buffer for hydrophilic drugs and a lipid film for lipophilic drugs when encapsulating a medicine.[2]

ii. Ultrasonic method

This method prepares small unilamellar vesicles with a diameter ranging from 15 to 25 nm. We employ two distinct sonication processes to ultrasonicate the glycerol dispersion of the lipid.

(a) Probe sonication: The sonicator's tip instantly approaches the glycerosomal dispersion. This approach involves a considerable energy input for lipid dispersion. Immerse the container containing the formulation in an ice/water bath to generate localized heat from the energy coupling at the probe's tip. Titanium easily detaches from sonicator tips, leading to contamination of the solution and requiring centrifugation for removal.[28]

(b) Bath sonication: To do bath sonication, you put a test tube with glycerosomal dispersion into the sonicator and sonicate the suspension for five to ten minutes, which is hotter than the lipid's critical solution temperature (Tc). Utilizing this technology in place of a probe sonicator makes temperature control straightforward.[5][28]

B) ORGANIC SOLVENT REPLACEMENT METHODS:

In this method lipid materials are co-solvated in organic solution, which is then dispersed into glycerol solution containing material to be entrapped within the vesicles. Following ways can be used to achieve this.

i. Reverse Phase Evaporation: This method initially creates a water-in-oil emulsion by sonicating a two-phase system containing phospholipids and cholesterol in an organic solvent like ethanol or isopropyl ether, or a combination of isopropyl ether and chloroform, in addition to an aqueous glycerol solution. The removal of the organic solvent under reduced pressure results in the formation of a viscous gel. We prepare the glycerosomes by removing the residual solvent through continuous rotary evaporation under reduced pressure. Additionally, this method makes it easier to create both large unilamellar and multilamellar vesicles, showing that they can effectively enclose large macromolecules. The primary disadvantage of this

approach is the exposure of the materials to organic solvents and short durations of sonication.[5]

ii. Solvent dispersion method:

It may be divided into two categories depending on the type of solvent used.

(a) Ether injection method: The ether injection method slowly adds a lipid solution that is dissolved in diethyl ether or a mixture of ether and methanol into a water-based or buffered glycerol solution that already has the materials that need to be encapsulated in it. We conduct this process at a temperature range of 55°C to 65°C or under reduced pressure. The main problem with the method is that the glycerosome population is not uniform; it can be anywhere from 70 to 190 nm in size. Also, the material that is trapped is exposed to organic solvents and high temperatures, which can damage it.[28][29][34]

(b) Ethanol injection method: In 1976, Batzri and Korn presented their findings on the ethanol injection method. This method entails dissolving lipid in ethanol and pushing it through a small aperture—potentially a syringe—into a surplus of aqueous medium. It is crucial to thoroughly mix an ethanolic lipid solution into an aqueous medium in a timely manner. Thorough mixing is necessary for the phospholipids to disperse in the water and for the ethanol to immediately dilute in the hydration medium. This technique offers a significant advantage by enabling the production of small liposomes, measuring less than 100 nm, without requiring sonication or extrusion. This is achieved by injecting a lipid solution that is dissolved in ether in water. Furthermore, the process generates diluted and uniform liposomes. Lipid solubility in ethanol constrains the volume of lipid incorporation into ethanol, thereby limiting the amount of ethanol usable in an aqueous medium. This represents a limitation of the ethanol injection method. While dialysis can remove it, ethanol remains in liposomes.[2]

C) SIZE TRANSFORMATION METHODS

i. Freeze thaw extrusion method: This method utilizes the process of freezing and thawing. The freeze-thaw method is applicable solely to crude phospholipids or to combinations of charged phospholipids, specifically those that display both positive and negative charges. We rapidly freeze and then thaw tiny unilamellar liposomes. They then undergo sonication to produce LUVs. This process leads to the fusion of SUV bilayers during freezing and thawing, resulting in the formation of LUVs. A rise in ionic strength or liposome concentration hinders the production of liposomes through this method. One limitation of the method is its inability to extract biological components, which require a lengthy and temperature-sensitive process.[28][34]

ii. The dehydration- rehydration method: In this method the empty buffer containing small unilamellar vesicles are rehydrated with the aqueous fluid containing the material to be entrapped after that they are dried. This leads to the formation of lipid dispersion in finely subdivided form. Glycerosomes obtained by this method are usually oligo-lamellar vesicles.[5]

3.1 CHARACTERIZATION OF GLYCEROSOMES: The glycerosomal formulation is characterized in terms of following parameters.

a) Vesicles size and size distribution:

When using glycerosomes for parenteral delivery, the size distribution plays a crucial role. The assessment of vesicle particle size employs various methodologies. These include light microscopy, electron microscopy (transmission electron microscope and scanning electron microscope), laser light scattering, photon correlation spectroscopy, gel permeation, and gel exclusion. The most accurate technique for measuring the size of glycerosomes is transmission electron microscopy, since it allows for the observation of each individual glycerosome and provides precise data on its size distribution.[35]

b) Vesicle shape and lamellarity:

Electron microscopy methods can evaluate the morphology and lamellarity of vesicles. We can assess lamellarity using freeze-fracture electron microscopy and 31P nuclear magnetic resonance studies. In addition to form and lamellarity, freeze-fracture and freeze-etch electron microscopy can analyze the surface morphology of glycerosomes.[36]

c) Percentage Encapsulation efficiency:

% Encapsulation Efficiency For the measurement of the amount of drug encapsulated in the vesicle, the dialysis method can be used. % encapsulation efficiency can be determined using the given formula.[6]

% Encapsulation efficiency = Drug Content / Initial Drug Content x 100

d) Drug release:

We can investigate the drug release process from glycerosomes using a well-calibrated Franz diffusion cell. Before starting research in living things, the glycerosomal formulation could be put through in vitro tests to see how it works and how well the drug is absorbed.[37]

e) Stability studies:

The stability of glycerosomes can be determined by dimensional analysis using Photon Correlation Spectroscopy technique, Zeta potential determination, Dynamic Laser Light Scattering and measuring the polydispersity index at various time intervals.[38]

f) Deformation Index Analysis:

For the determination of the deformation index, glycerosomal preparations are supposed to pass through an extruder having a pore size smaller than the mean diameter of vesicles.[28]

4. THERAPEUTIC APPLICATIONS OF GLYCEROSOMES:

When a conventional dosage form fails to provide a desired therapeutic effect, then new drug delivery systems are developed. Glycerosomes are among such systems which provide a superior therapeutic efficacy and safety in comparison to presently available formulations.[22]

Some of the major clinical/therapeutic applications of glycerosomes in drug delivery are as follows.

S.No.	Parameters	Key Observations	Reference
1	Site specific drug delivery	Site-specific targeting can deliver the maximum amount of drugs to the targeted (diseased) site while minimizing exposure to healthy tissues. Encapsulating the drug in glycerosomes facilitates both active and passive drug targeting, thereby ensuring a safe and effective therapeutic approach. In systemic administration, glycerosomes demonstrate an enhanced ability to recognize and bind to target cells with increased specificity.	[2]
2	Oral Drug Delivery	Glycerosomes enhance the stability and bioavailability of orally administered drugs, focusing on the gastrointestinal tract or systemic circulation. They are very effective for administering poorly soluble or sensitive medications.	[48]
3	Glycerosomes in dermatology	**Skin Disorders:** Glycerosomes make it easier for drugs to be delivered through the skin, which makes them useful for treating psoriasis, eczema, and fungal infections. **Wound healing**: The administration of growth factors, antibiotics, or anti-inflammatory agents to wound sites may enhance healing and avert infections.	[39]
4	Cancer Therapy	By integrating ligands or antibodies specific to cancer cell markers, one can design glycerosomes to target tumors. They improve the administration of chemotherapy to tumor tissues, reducing systemic toxicity.	[40]
5	Ocular Drug Delivery	Glycerosomes may target particular ocular regions, including the cornea and retina, for the treatment of disorders such as glaucoma, macular degeneration, and uveitis. Their biocompatibility and mucoadhesive characteristics enhance medication retention and absorption in the ocular environment.	[41]
6	Glycerosomes for pulmonary targeting of drugs	Specific delivery of glycerosomes to pulmonary tissues aids in the treatment of respiratory conditions such as asthma, chronic obstructive	[42]

		pulmonary disease (COPD), and pulmonary infections. They provide extensive lung infiltration and controlled distribution of therapeutic agents.	
7	Vaccination	Glycerosomes serve as adjuvants and delivery systems for vaccines, enhancing immune responses by directing attention to antigen-presenting cells. Their biocompatibility makes them appropriate for both subcutaneous and mucosal vaccination administration.	[43]
8	Enhanced antimicrobial efficacy/ safety	Glycerosomes encapsulate antimicrobial agents for two primary reasons. Initially, they safeguard the encapsulated drug from enzymatic degradation. Secondly, the lipid composition of the vesicles enhances the cellular uptake of antimicrobials in microorganisms, thereby minimizing the required dosage and the likelihood of toxicity. Various antimicrobial agents, including resveratrol, gallic acid, tolnaftate, and citrus lemon extract, were effectively incorporated into glycerosomes, demonstrating enhanced antimicrobial efficacy against cultured plankton from different species of Streptococcus and Lactobacillus.	[2]
9	Neurological Disorders	Glycerosomes help deliver drugs to specific areas of the brain by crossing the blood-brain barrier (BBB). This makes it possible to treat diseases like Alzheimer's, Parkinson's, and brain cancer. We use them to administer neuroprotective drugs or small interfering RNA (siRNA).	[44]
10	Glycerosomes for the delivery of anti-inflammatory agents	Anti-inflammatory drugs exhibit a wide range of potential side effects. One potential approach to enhance the therapeutic efficacy of these drugs may involve glycerosomal encapsulation. Glycerosomes have effectively integrated nonsteroidal anti-inflammatory drugs such as diclofenac, celecoxib, and cupferron. Recent results indicate that glycerosomes demonstrate significant biocompatibility with human keratinocytes.	[2]
11	Glycerosomes for Topical Delivery	Glycerosomes facilitate the transport of active compounds in cosmetic and dermatological	[45]

		formulations, enhancing skin hydration and suppleness. Anti-aging therapies and dermal revitalization utilize them.	
12	Targeted Delivery to Infected Tissues	Glycerosomes may deliver antimicrobial drugs directly to infected tissues, making them more effective and lowering resistance by increasing drug concentrations in those areas.	[46]
13	Intrasynovial drug delivery	Using glycerosomes to get drugs into the synovium could help treat joint problems like osteoarthritis (OA), rheumatoid arthritis (RA), and synovitis. The synovial cavity in joints presents a significant challenge for effective drug administration because synovial fluid dynamics rapidly remove therapeutic drugs and the synovial membrane has limited permeability. Glycerosomes offer specific advantages in tackling these challenges. 1. Enhanced Retention in Synovial Cavity 2. Controlled and Sustained Release 3. Improved Penetration 4. Reduced Systemic Side Effects 5. Biocompatibility and Safety	[47]
14	Sustained release drug delivery	Glycerosomes serve to facilitate a sustained release of drugs, ensuring a consistent drug level over a designated period while minimizing side effects. Glycerosomes encapsulate rifampicin and betamethasone to achieve sustained release and optimize the drug release rate in vivo.	[2]
15	Intra-follicular administration	The intra-follicular administration of drugs may serve as a viable therapeutic strategy for addressing skin conditions, including hair loss. The new glycerosomal formulation makes it easier for difficult-to-absorb substances like minoxidil to be applied to the skin, where they can work directly on hair follicles and sebaceous glands.	[2]

5. EXAMPLES OF SOME GLYCEROSOMAL FORMULATIONS

In this Some glycerosomal formulations and their method of preparations are involved in two ways:

1. Phytoconstituent
2. Synthetic Drugs

Table 1. List of some glycerosomal formulation of phytoconstituent and their method of preparation:

S. No.	Type of Formulation	Compound	Method	Glycerol Used (%)	Uses	Ref.
1	Glycerosomes	Quercetin	Thin film hydration technique	10–50	Antioxidants, a protective effect against oxidative stress and skin damages	[49]
2	Glycerosomes	Curcumin	Direct hydration of phospholipids	10-50	cytotoxicity, antioxidant, and anti-inflammatory	[15]
3	Glycerosomes	Citrus limon (L.) extract Osbeck var. pompia	Thin film dispersion ultrasonic method	25-50	Antioxidant and antibacterial	[50]
4	Glycerosomes	Fisetin	Thin Film Hydration method	20-40	Transdermal delivery	[51]
5	Glycerosomes	Melissa officinalis L	Thin Layer Evaporation Method	……	Anti-HSV	[52]
6	Hyalurosome and Glycerosome	Zingiber officinalis L.	Thin film dispersion ultrasonic method	…….	In the treatment of rhinitis and rhinosinusitis	[53]
7	Silver nanoparticles polyvinylpyrrolidone based glycerosomes (GPVP-AgNPs)	Diospyros kaki L	Chemical synthesis	1.5	Antimicrobial	[54]
8	Glycerosomes	Plumbagin	Thin film hydration method	30	Antioxidant and skin cancer therapy	[55]

9	Glycerosomes	Hypericum scruglii Extract	Thin film hydration method	25	Skin lesions	[56]

Table 2. **List of some glycerosomal formulations of synthetic drugs and their method of preparation.**

S. No.	Type of Formulation	Synthetic Drug	Method	Glycerol Used (%)	Uses	Ref.
1	Glycerosomes	Diclofenac	Thin film hydration method	10-30	Anti-inflammatory, used in transdermal delivery	[16]
2	Hexosomes, Glycerosomes, and Ethosomes	Tretinoin	Thin film dispersion ultrasonic method	20	Anti-inflammatory, Skin penetration, and antirosacea treatment	[57]
3	Glycerosomes, TMC glycerosomes, and HY-glycerosomes	Rifampicin	Direct hydration	1	cytotoxicity, antibacterial	[58]
4	Glycerosomes	Minoxidil	Lipid thin film hydration method	10-50	Formulation study	[59]
5	Glycerosomes	Diclofenac	Thin film hydration method	10-30	Transdermal delivery	[34]
6	Liposomes, glycerosomes and transferosomes	Sertaconazole nitrate	Thin film hydration method	20	Transdermal delivery	[60]
7	Glycerosomes	paeoniflorin	Reverse phase evaporation method	10	Transdermal delivery	[13]
8	Glycerosomes	Celecoxib and Cupferron	Lipidic film hydration technique.	20-40	Anti-inflammatory	[32]

9	Proteo-glycerosomes	Asolectin	…….	20	Anti-histaminic activity	[61]
10	Glycerosome	Triptolide	Injection method	20	Enhance transdermal delivery	[33]
11	Glycerosomes	Lacidipine	Thin film hydration method	10-40	Enhance intranasal delivery without any inflammation responses	[62]

6. GLYCEROSOME BASED DRUG DELIVERY NANOCARRIERS: Polymeric glycerosomes are synthesized by including an appropriate polymer into the glycerosome formulation. The polymer addition occurred during the hydration phase. This resulted in the development of polymer-coated glycerosomes. These vesicles inside create a network of polymers, enhancing the in vivo properties of the system.[15][58] The principal characteristics of polymeric glycerosomes include greater biocompatibility, improved drug deposition at the target site, evasion of first-pass metabolism, targeted delivery to the lungs, and inherent safety and nontoxicity. These formulations may be readily transformed into aerosol form, hence facilitating pulmonary drug administration.

TABLE 3: GRANTED PATENT OF GLYCEROSOMES Adapted from ref. (2)

Title	Patent Number	Type	Filed	Date of Patent	Assignee	Inventor
Glycerosomes and use thereof in pharmaceutical and cosmetic preparations for topical application	8778367	Grant	March 8, 2010	July 15, 2014	PRIGEN S.R.L.	Marco Zaru, Maria Letizia Manca, Anna Maria Fadda, Gaetano Orsini

7. CHALLENGES AND LIMITATIONS

Vesicular drug delivery systems (VDDS) exhibit remarkable potential, yet they encounter significant challenges.

A) Manufacturing Challenges and Scalability

1. Scaling Up Production: Increasing the production of vesicular drug delivery systems, such as liposomes, presents a considerable difficulty. Key challenges include maintaining vesicle size, ensuring batch-to-batch uniformity, and avoiding contamination.

2. Cost Effectiveness: Mass manufacturing often encounters cost-related challenges that impact economic viability. High manufacturing costs and stability issues are the main problems.

B) Regulatory Hurdles for Novel Vesicular Systems

The regulatory environment for vesicular drug delivery devices is complex. The FDA and EMA, among others, impose stringent requirements on liposome formulations to ensure medicine safety, effectiveness, and quality. Also, the lack of standardization makes it harder to approve new systems like archaeosomes and glycerosomes because they need a lot of preclinical and clinical studies to make sure they are biocompatible and have potential therapeutic benefits. These studies take a lot of time and resources.

Overcoming these obstacles necessitates continuous research to optimize formulation methods, augment stability, boost targeting efficacy, and guarantee safety in order to fully realize the promise of VDDS in clinical applications.

8. FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

Potential future paths for vesicular systems may include nanotechnology and biotechnology. For instance, Archaeosomes are used in immunotherapy and glycerosomes are used to deliver genes. This system can be used in a lot of different ways under further research.

9. CONCLUSION

Various concentrations of glycerol form glycerosomes, a novel vesicular structure. These structures are appropriate for penetrating skin tissues. Moreover, the ability to enhance skin penetration, increase encapsulation efficiency, and produce flexible, more fluidic vesicles makes the glycerosomal drug administration method fundamentally useful.[2] This method utilizes glycerol as a carrier that modifies the penetration capability across epidermal layers.[6][63] Another benefit of glycerosomal formulation is the simplicity of preparation at ambient temperature. Encapsulating a larger amount of pharmaceuticals results in delayed drug release due to osmotic imbalance on both sides. Nonetheless, these configurations have shown stability, smoothness, trapping, and consistency in recent years. Research on in vivo administration is lacking, despite glycerosomes' promise as drug delivery nanocarriers. Future research must focus on merging relevant in vitro and in vivo evaluations with biophysical analyses. This will enhance our understanding of the mechanisms by which these nano-self-assemblies release and encapsulate medicines, and explore their potential application in clinical settings. In the next years, we expect an increase in literature on the in vivo fates of these nano-self-assemblies after diverse administration methods, given their significance in the advancement of drug nanocarriers. Although we have adequately substantiated the preliminary preclinical research, their clinical applications continue to pose significant challenges. Because of this, needs to be more excitement about the clinical uses of glycerosomes to prove that they are the best tool for nanocarrier drug delivery systems.[6][28]

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