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LIPOSOMES USING HERBAL ACTIVE INGREDIENTS AS DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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ABSTRACT

Herbal medicines and phytoconstituents have been extensively used in traditional and modern medicine due to their broad spectrum of pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, cardioprotective, and neuroprotective effects. Despite their therapeutic potential, many herbal active ingredients suffer from poor aqueous solubility, instability, rapid metabolism, low permeability, and poor bioavailability, limiting their clinical application. Liposomes have emerged as promising vesicular drug delivery systems capable of improving the therapeutic efficiency of herbal bioactives. Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic phytoconstituents, thereby enhancing solubility, stability, bioavailability, and targeted delivery. Herbal liposomal formulations have demonstrated significant improvements in pharmacokinetic and pharmacodynamic properties while reducing toxicity and improving site-specific drug delivery. This review discusses the structure, classification, preparation methods, characterization, advantages, limitations, and applications of liposomes containing herbal active ingredients. Special emphasis is placed on liposomal formulations of curcumin, silymarin, quercetin, resveratrol, berberine, catechins, and other phytochemicals. Recent advances in targeted liposomes, stealth liposomes, phytosomes, and nanoliposomal systems are also highlighted. Furthermore, challenges related to stability, scalability, regulatory approval, and future prospects of herbal liposomal drug delivery systems are discussed.

1. Introduction

Herbal medicines have played a vital role in healthcare systems for centuries and continue to gain global attention due to their therapeutic efficacy and relatively low toxicity. Plant-derived bioactive compounds such as flavonoids, alkaloids, terpenoids, polyphenols, tannins, and glycosides possess significant pharmacological activities against various chronic and infectious diseases. However, many herbal active constituents exhibit poor water solubility, low permeability, instability in gastrointestinal fluids, rapid metabolism, and low systemic bioavailability, which limit their therapeutic performance[1].

To overcome these limitations, various novel drug delivery systems have been developed, including nanoparticles, microspheres, nanoemulsions, solid lipid nanoparticles, dendrimers, phytosomes, and liposomes. Among these, liposomes are one of the most extensively investigated vesicular carriers for delivering herbal active ingredients. Liposomes are phospholipid vesicles composed of one or more lipid bilayers surrounding an aqueous core. Due to their amphiphilic nature, liposomes can encapsulate both hydrophilic and lipophilic compounds efficiently[2].

Liposomal systems provide several advantages such as enhanced drug solubility, protection against degradation, controlled release, reduced toxicity, prolonged circulation time, and targeted drug delivery. Herbal liposomes have shown promising applications in cancer therapy, anti-inflammatory treatment, neurodegenerative disorders, antimicrobial therapy, liver diseases, and cosmetic formulations[3].

In recent years, phytosome technology, a specialized lipid-based delivery system involving complexation of phytoconstituents with phospholipids, has gained attention for improving oral bioavailability and therapeutic efficacy of herbal drugs[4].

This review comprehensively discusses the role of liposomes in the delivery of herbal active ingredients, including formulation approaches, applications, advantages, limitations, and future perspectives[5].

2. Liposomes: Definition and Structure

Liposomes are microscopic spherical vesicles composed of natural or synthetic phospholipid bilayers enclosing an aqueous compartment. They were first described by Alec Bangham in 1965 and have since become important carriers in pharmaceutical drug delivery.

The basic components of liposomes include:

- Phospholipids
- Cholesterol
- Surface modifiers
- Active pharmaceutical ingredients

Structurally, liposomes consist of:

- Hydrophilic aqueous core
- Hydrophobic phospholipid bilayer

Hydrophilic drugs are entrapped within the aqueous core, whereas lipophilic compounds are incorporated into the phospholipid membrane.

Common phospholipids used include:

- Phosphatidylcholine
- Phosphatidylethanolamine
- Sphingomyelin
- Lecithin

Cholesterol is often added to improve membrane rigidity and stability.

3. Need for Liposomal Delivery of Herbal Active Ingredients

Many phytoconstituents exhibit poor pharmacokinetic properties due to:

- Low aqueous solubility
- Poor membrane permeability
- Chemical instability
- Extensive first-pass metabolism
- Rapid elimination

Examples include:

- Curcumin
- Quercetin
- Silymarin
- Resveratrol
- Berberine
- Catechins

These limitations reduce therapeutic efficacy and necessitate high doses.

Liposomal delivery systems help overcome these challenges by:

- Enhancing solubility
- Improving absorption
- Protecting phytoconstituents from degradation
- Providing sustained release
- Enhancing tissue targeting
- Reducing toxicity

4. Classification of Liposomes

Liposomes can be classified based on size, lamellarity, composition, and surface characteristics.

4.1 Based on Lamellarity

a) Unilamellar Vesicles

Contain a single phospholipid bilayer.

- Small unilamellar vesicles (SUVs)
- Large unilamellar vesicles (LUVs)

b) Multilamellar Vesicles (MLVs)

Contain multiple concentric phospholipid bilayers.

4.2 Based on Surface Characteristics

a) Conventional Liposomes

Simple phospholipid vesicles without surface modification.

b) Stealth Liposomes

Surface-coated with polyethylene glycol (PEG) to avoid reticuloendothelial clearance.

c) Targeted Liposomes

Modified with ligands, antibodies, or peptides for site-specific targeting.

d) Stimuli-Responsive Liposomes

Respond to pH, temperature, or enzymes.

4.3 Specialized Liposomal Systems

- Phytosomes
- Transfersomes
- Ethosomes
- Niosomes
- Immunoliposomes

5. Phytosomes: Specialized Herbal Liposomes

Phytosomes are phospholipid complexes formed between phytoconstituents and phospholipids. Unlike conventional liposomes where the drug is merely entrapped, phytosomes involve molecular complexation between phytochemicals and phospholipids.

Advantages of Phytosomes

- Improved bioavailability
- Enhanced membrane permeability
- Better stability
- Improved absorption
- Enhanced pharmacological effect

Common phytosomal formulations include:

- Curcumin phytosomes
- Silymarin phytosomes
- Ginkgo biloba phytosomes
- Green tea phytosomes

Phytosomes are particularly effective for polyphenolic compounds with poor lipid solubility.

6. Preparation Methods of Herbal Liposomes

Several methods are used for preparation of herbal liposomes.

6.1 Thin Film Hydration Method

Most commonly used technique.

Procedure:

1. Dissolve phospholipids and cholesterol in organic solvent.
2. Evaporate solvent to form thin lipid film.
3. Hydrate with aqueous herbal extract solution.
4. Sonicate to reduce vesicle size.

Advantages:

- Simple
- Cost-effective
- High encapsulation efficiency

6.2 Reverse Phase Evaporation Method

Used for high aqueous drug loading.

6.3 Ethanol Injection Method

Lipids dissolved in ethanol are injected into aqueous phase.

Advantages:

- Easy scale-up
- Small particle size

6.4 Sonication Method

Used to reduce vesicle size and obtain SUVs.

6.5 Microfluidization Method

Produces uniform nanosized liposomes.

7. Characterization of Herbal Liposomes

Characterization is essential for ensuring stability and performance.

Important Parameters

7.1 Particle Size and Distribution

Measured using dynamic light scattering.

7.2 Zeta Potential

Indicates surface charge and stability.

7.3 Entrapment Efficiency

Determines amount of herbal drug encapsulated.

7.4 Morphology

Evaluated by:

- TEM
- SEM
- AFM

7.5 In Vitro Drug Release

Evaluates release kinetics.

7.6 Stability Studies

Assesses storage stability and leakage.

8. Herbal Active Ingredients Used in Liposomal DDS

8.1 Curcumin Liposomes

Curcumin from Turmeric possesses:

- Anticancer
- Antioxidant
- Anti-inflammatory activities

However, curcumin exhibits poor water solubility and rapid metabolism.

Liposomal curcumin formulations improve:

- Bioavailability
- Cellular uptake
- Antitumor activity
- Stability

Curcumin liposomes have shown promising applications in:

- Breast cancer
- Colon cancer
- Alzheimer's disease
- Inflammatory disorders

8.2 Silymarin Liposomes

Silymarin extracted from Milk Thistle exhibits hepatoprotective activity.

Limitations:

- Poor solubility
- Low oral absorption

Liposomal and phytosomal silymarin formulations significantly improve:

- Liver targeting
- Bioavailability
- Antioxidant activity

Silymarin phytosomes are among the most successful commercial herbal lipid formulations.

8.3 Quercetin Liposomes

Quercetin is a flavonoid with:

- Antioxidant
- Anticancer
- Cardioprotective properties

Challenges:

- Poor aqueous solubility
- Low permeability

Liposomal quercetin improves:

- Stability
- Cellular delivery
- Antitumor efficacy

8.4 Resveratrol Liposomes

Resveratrol possesses:

- Anti-aging
- Antioxidant
- Cardioprotective activity

Liposomal formulations enhance:

- Solubility
- Bioavailability
- Sustained release

8.5 Berberine Liposomes

Berberine demonstrates:

- Antidiabetic
- Antimicrobial
- Anticancer effects

Liposomal berberine enhances intestinal absorption and therapeutic activity.

8.6 Catechin and EGCG Liposomes

Catechins from Green Tea exhibit strong antioxidant activity.

Liposomal EGCG formulations improve:

- Stability
- Controlled release
- Anticancer potential

9. Applications of Herbal Liposomes

9.1 Cancer Therapy

Liposomal herbal formulations enhance tumor targeting and reduce systemic toxicity.

Applications include:

- Curcumin liposomes
- Quercetin liposomes
- Resveratrol liposomes

Advantages:

- Enhanced permeability and retention effect
- Reduced toxicity
- Controlled release

9.2 Anti-inflammatory Therapy

Herbal liposomes improve delivery of anti-inflammatory phytochemicals to inflamed tissues.

Examples:

- Curcumin
- Boswellic acid
- Gingerol

9.3 Neuroprotective Applications

Liposomes facilitate brain delivery of phytoconstituents.

Applications:

- Alzheimer's disease
- Parkinson's disease
- Neuroinflammation

9.4 Hepatoprotective Therapy

Silymarin liposomes improve liver targeting and hepatoprotection.

9.5 Antimicrobial Therapy

Herbal liposomes enhance penetration into microbial biofilms and infected tissues.

Examples:

- Essential oil liposomes
- Garlic extract liposomes

9.6 Cosmetic Applications

Liposomal herbal formulations are widely used in cosmetics for:

- Anti-aging
- Skin hydration
- UV protection

Examples:

- Aloe vera liposomes
- Green tea liposomes

10. Advantages of Herbal Liposomes

10.1 Enhanced Bioavailability

Liposomes improve oral absorption and systemic availability.

10.2 Improved Stability

Protect herbal compounds from oxidation and degradation.

10.3 Controlled Release

Provide sustained drug release.

10.4 Reduced Toxicity

Minimize exposure to healthy tissues.

10.5 Targeted Drug Delivery

Improve site-specific accumulation.

10.6 Biocompatibility

Phospholipids are biodegradable and non-toxic.

11. Limitations of Herbal Liposomes

Despite advantages, herbal liposomes have certain limitations.

11.1 Physical Instability

Problems include:

- Aggregation
- Fusion
- Leakage

11.2 Chemical Instability

Phospholipids undergo oxidation and hydrolysis.

11.3 High Production Cost

Manufacturing and purification are expensive.

11.4 Scale-Up Challenges

Industrial production requires sophisticated technology.

11.5 Short Shelf Life

Storage stability remains challenging.

12. Recent Advances in Herbal Liposomal DDS

12.1 Nanoliposomes

Nanosized liposomes provide:

- Enhanced penetration
- Better bioavailability
- Improved targeting

12.2 Stealth Liposomes

PEGylated liposomes prolong circulation time.

12.3 Targeted Liposomes

Ligand-conjugated liposomes enable receptor-mediated delivery.

12.4 Stimuli-Responsive Liposomes

Triggered release under:

- pH change
- Temperature
- Enzymatic activity

12.5 Combination Therapy

Liposomes co-deliver herbal compounds with synthetic drugs for synergistic action.

13. Regulatory and Safety Considerations

Regulatory approval of herbal liposomal products requires:

- Toxicity evaluation
- Stability assessment
- Quality control
- Reproducibility studies

Challenges include:

- Variability of herbal extracts
- Standardization issues
- Lack of harmonized guidelines

14. Future Prospects

Future research should focus on:

- Large-scale manufacturing
- Clinical translation
- Personalized herbal nanomedicine
- Smart targeted systems
- AI-assisted formulation design
- Improved regulatory frameworks

Integration of nanotechnology with herbal medicine may revolutionize treatment strategies for chronic diseases and cancer[6-11].

15. Conclusion

Liposomes represent highly promising carriers for herbal active ingredients due to their ability to improve solubility, stability, bioavailability, and targeted delivery of phytoconstituents. Herbal liposomal systems including conventional liposomes, nanoliposomes, stealth liposomes, and phytosomes have demonstrated remarkable therapeutic potential in cancer therapy, anti-inflammatory treatment, neuroprotection, hepatoprotection, and cosmetic applications. Phytochemicals such as curcumin, silymarin, quercetin, resveratrol, berberine, and catechins show significantly enhanced pharmacokinetic and pharmacodynamic

properties when delivered through liposomal systems. Although challenges related to stability, standardization, regulatory approval, and scalability persist, ongoing advancements in nanotechnology and pharmaceutical engineering are expected to facilitate successful clinical translation of herbal liposomal drug delivery systems. Herbal liposomes therefore offer an innovative and effective platform for future pharmaceutical and nutraceutical applications.

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