



INNOVATIVE HERBAL DRUG DELIVERY SYSTEM

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ABSTRACT:

Advancements in herbal formulations, utilizing advanced delivery systems like polymeric nanoparticles, liposomes, phytosomes, and transfersomes, have significantly improved the effectiveness of plant-based medicines. These novel systems enhance solubility, bioavailability, and stability, protect against toxicity and degradation, and provide sustained release and better pharmacological effects. A key innovation is Phytosome technology, which combines phospholipids with plant extracts to create lipid-compatible complexes that boost bioavailability and stability.

Recent research highlights the advantages of modern drug delivery systems (NDDS) in herbal medicine, showcasing improved therapeutic outcomes compared to traditional methods. These systems, including liposomes and solid lipid nanoparticles, enhance absorption and bioavailability. While challenges in extraction and standardization of herbal medicines have previously hindered innovation, the rise of herbal excipients—affordable, biodegradable, and stable plant-derived compounds—has enabled more effective delivery systems.

These innovations are particularly beneficial in addressing common health issues and enhancing treatments, including more effective anticancer therapies, underscoring the potential of herbal medicines in modern medicine.

KEYWORDS: Innovative Herbal Formulation Technologies, Herbal Compound Nanoencapsulation, Precise Phytochemical Targeted Delivery, Intelligent Herbal Drug Carriers, Sustained Release Systems for Herbal Medicines

INTRODUCTION:

Recent advancements in herbal medicine have led to the development of novel drug delivery systems (NDDS), addressing limitations in traditional formulations that struggle to provide targeted delivery and sustained release. Nano-sized carriers like polymeric nanoparticles, liposomes, phytosomes, solid lipid nanoparticles, and nanoemulsions offer several advantages for herbal drugs, such as improved solubility, increased bioavailability, reduced toxicity, enhanced pharmacological effects, and sustained release. These systems also stabilize the formulation, enhance tissue targeting, and protect against degradation.

Compared to conventional methods, NDDS are more efficient in delivering herbal medicines at precise rates and targeted sites, minimizing side effects. For instance, liposomes can focus higher drug concentrations on tumors, reducing damage to healthy cells. Phytosomes, which combine phosphatidylcholine with herbal extracts like Ginseng, improve absorption over traditional approaches. Other systems, such as microspheres and polymeric nanoparticles, also contribute to the effectiveness of herbal treatments. This review highlights the potential of these advanced drug delivery systems to improve the application and therapeutic outcomes of herbal medicines.

HERBAL DRUGS:

Herbal formulations are dosage forms that contain one or more herbs or processed plant materials, carefully measured to provide specific nutritional, cosmetic, or therapeutic benefits. These preparations are designed for use in diagnosing, treating, or altering the physiological or structural conditions of humans or animals. Herbal medicines are created by subjecting whole plants, plant parts, or plant extracts to various processes such as fermentation, distillation, expression, fractionation, extraction, purification, and concentration. The end products include tinctures, extracts, essential oils, squeezed juices, refined resins, and powdered plant materials.

Advantages of Herbal Drugs:

- Minimal risk of side effects
- Proven effectiveness
- Lower cost compared to conventional treatments
- Easy availability across a wide range of regions

Importance of Novel Herbal Drug Delivery Systems:

Innovative drug delivery systems represent a groundbreaking approach to overcoming the limitations of traditional drug administration methods. While the rich tradition of Ayurvedic knowledge in India holds great potential, the effectiveness of herbal medicines has often been compromised by outdated delivery techniques. Incorporating novel drug delivery technologies into herbal medicine can significantly enhance their therapeutic effects and reduce potential side effects. This is particularly important for addressing complex health issues, where combining Ayurvedic remedies with advanced delivery systems can improve outcomes.

For a long time, herbal medicines were overlooked for novel formulation development due to challenges in standardization, extraction, and identifying specific therapeutic components, particularly in complex polyherbal systems. However, modern phytopharmaceutical research is now equipped to meet the scientific standards necessary for integrating herbal medicines into cutting-edge delivery systems like liposomes, nanoparticles, microemulsions, solid dispersions, and solid lipid nanoparticles. This includes understanding the pharmacokinetics, mechanism of action, optimal dosage, and target sites of herbal components.

These advanced drug delivery systems aim to reduce drug loss, prevent degradation, minimize side effects, and enhance bioavailability, ensuring that herbal medicines are more effective and concentrated at their intended sites of action.

Potential of Novel Drug Delivery for Herbal Drugs:

Phytopharmaceuticals are pharmaceutical products derived from botanical compounds rather than synthetic chemicals. Natural plant-derived chemicals are typically metabolized more easily and quickly by the body, leading to fewer side effects compared to their synthetic counterparts. As a result, herbal drugs enhance bloodstream absorption and offer more effective treatments with minimal adverse reactions. In contrast, chemical-based drugs can trigger undesirable side effects, as the body often rejects non-natural substances, leading to reactions ranging from mild discomfort to severe, potentially life-threatening conditions.

Numerous studies have explored lipid-based drug delivery systems, highlighting their potential for targeted and controlled medication release. One such system, pharmacosomes, involves drug-loaded phospholipid complexes that bond with phospholipids and contain active hydrogen. These complexes improve the biopharmaceutical properties of the drug, thereby increasing its bioavailability. Phytosomes, a similar system, are created by binding plant-derived compounds (such as those from *Silybum Marianum*, Ginseng, and Ginkgo Biloba) with phospholipids. This phytolipid delivery system, due to its high lipophilicity, improves both the bioavailability and therapeutic effectiveness of these plant extracts.

Phytosomes are especially beneficial for treating conditions like acute liver disorders, whether caused by infections or metabolic issues, due to their enhanced pharmacokinetic and pharmacological properties. Through a specialized process, active components of the herbal extracts, such as terpenoids and flavonolignans, are molecularly attached to phospholipids like phosphatidylcholine. This unique structure increases the efficacy and absorption of herbal medicines, making phytosomes valuable in both medicinal and cosmetic applications. However, much remains to be discovered about their full medical potential.

Ideal Features of Drug Delivery Systems:

- **Targeted Delivery:** The system should precisely direct the medication to the intended site of action.
- **Biochemical Inertness:** It must be non-toxic and non-immunogenic, ensuring it does not provoke harmful reactions in the body.
- **Stability:** The system should be chemically and physically stable in both in vitro and in vivo conditions.
- **Consistent and Localized Drug Distribution:** The drug should be distributed uniformly and exclusively to the target cells or organs.
- **Controlled Release:** The system should provide a predictable and controlled rate of drug release.
- **Unaltered Mechanism of Action:** The therapeutic effect of the drug should remain unaffected by the delivery system.
- **Therapeutic Release:** The system should release a sufficient therapeutic dose of the drug.
- **Minimal Drug Leakage:** Drug leakage during transit should be minimized to prevent unintended exposure to other areas.
- **Biodegradability:** The carrier should be biodegradable or easily eliminated by the body, without causing harm or triggering immune responses.
- **Efficiency and Cost-Effectiveness:** The system should be easily reproducible and cost-effective to produce and distribute.

Current Challenges in Modernizing Herbal Formulations:

- **Managing Risk Levels:** Ensuring that herbal formulations remain within acceptable safety and risk parameters.
- **Addressing Uncertainty:** Effectively communicating the uncertainties associated with herbal treatments.
- **Pharmacological, Toxicological, and Clinical Documentation:** Ensuring comprehensive documentation of the pharmacological, toxicological, and clinical aspects of herbal formulations.
- **Pharmacovigilance:** Monitoring the safety of herbal products and tracking adverse effects.

- **Understanding the Mechanisms of Action:** Gaining a clearer understanding of how harmful additives or ingredients may influence the efficacy of herbal formulations.
- **Assessing Drug Interactions:** Evaluating potential interactions between herbal drugs and other medications.
- **Clinical Trial Evaluation:** Selecting appropriate participants for clinical trials and ensuring their availability for research studies.
- **Standardization:** Establishing standardized methods for the preparation, dosage, and quality control of herbal formulations.
- **Assessing Safety and Efficacy:** Conducting thorough evaluations to assess both the safety and therapeutic effectiveness of herbal medicines.

Advantages and Disadvantages of NDDS:

Advantages:

- **Targeted Delivery:** NDDS allows for precise targeting of the drug to specific sites in the body, enhancing therapeutic outcomes.
- **Increased Surface Area:** These systems improve the surface area of drugs, leading to faster absorption and quicker onset of action.
- **Improved BBB Penetration:** Nanoparticles in NDDS can effectively penetrate the Blood Brain Barrier (BBB), enabling the delivery of drugs to the brain.
- **High Efficacy:** NDDS typically offers higher therapeutic effectiveness due to controlled and targeted release.
- **Enhanced Stability:** These systems improve the stability of herbal drugs, preventing degradation and ensuring consistent performance.
- **Long-Term Stability:** NDDS protect the active components of plants from degradation, extending the shelf life and potency of herbal medicines.

Disadvantages:

- **Drug Leakage:** There is a risk of the entrapped drugs leaking from the delivery system, reducing effectiveness.
- **Unpredictable Effects:** The therapeutic effects of NDDS can sometimes be unpredictable, leading to variable outcomes.
- **Physical Instability:** The physical stability of the delivery system may be compromised under certain conditions, affecting its performance.
- **Limited Bioacceptability:** The body may have limitations in accepting or tolerating certain drug delivery systems, affecting their overall effectiveness.

TYPES OF NOVEL DRUG DELIVERY SYSTEMS:

LIPOSOMES:

Liposomes are spherical, bilayered vesicles that encapsulate an aqueous core, with a lipid membrane primarily composed of natural or synthetic phospholipids. These particles contain a solvent inside them, where it can diffuse freely. Liposomes can have one or multiple concentric layers, which are typically formed by polar lipids. These lipids have both hydrophilic (water-attracting) and lipophilic (fat-attracting) groups within the same molecule. However, unlike detergents, lipids with larger hydrophobic components tend to form bilayers that close into liposomes or lipid vesicles, rather than micelles. When polar lipids interact with water, they self-assemble into these colloidal particles.

Liposomes can be produced in various sizes, from single to multilayered structures, and their name reflects their composition, not their size. These vesicles do not typically contain water, but instead are designed to encapsulate drugs within their lipid layers, making them effective for targeted drug delivery, particularly for diseases like cancer. Liposomes are usually formed by methods like sonic disruption of biological membranes and range from 0.05 to 5.0 μm in diameter. They are biocompatible, biodegradable, and can carry a variety of drugs, depending on their lipophilicity, either within the phospholipid bilayer or at the interface between the layers.

Herbal drugs can also be encapsulated in liposomes, allowing for improved delivery and targeted release. These liposomal formulations can be used to enhance the therapeutic effects of herbal medicines by improving their stability, bioavailability, and controlled release.

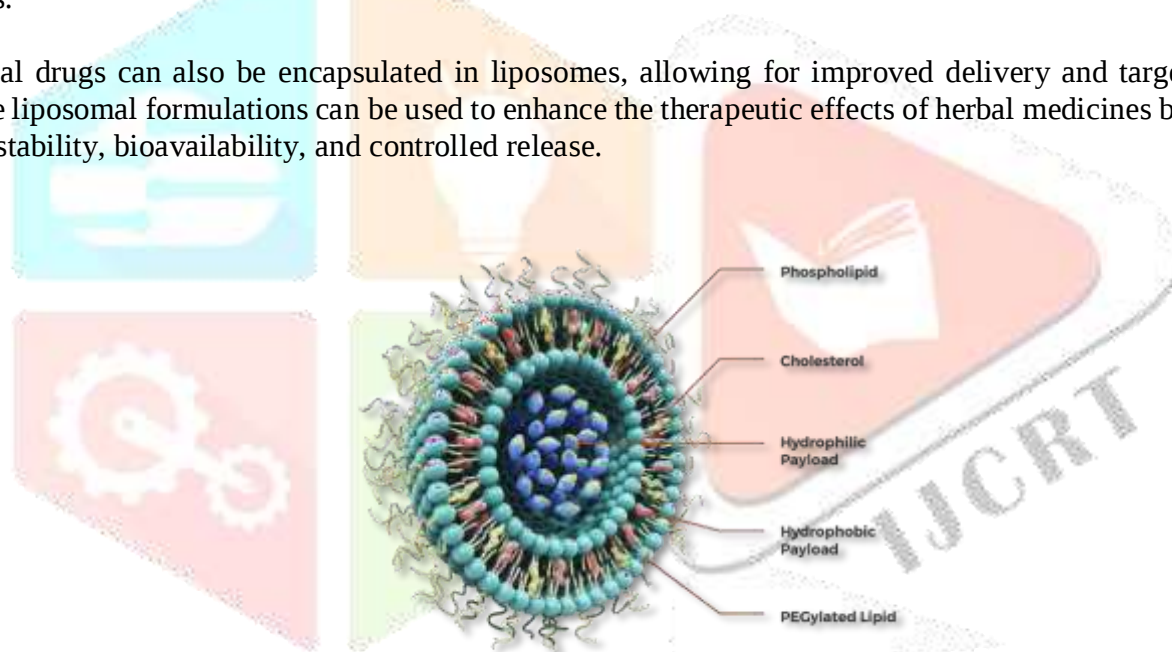


Fig no 1- Liposomes

Advantages of Liposomes

1. **Targeted Delivery:** Liposomal formulations, such as liposomal doxorubicin, can specifically target tumor tissues through passive targeting, improving treatment accuracy.
2. **Enhanced Therapeutic Effectiveness:** Liposomes increase the therapeutic index, making the treatment more effective.
3. **Improved Stability:** Encapsulating drugs in liposomes enhances their stability, protecting the active compounds from degradation.
4. **Reduced Toxicity:** Liposomal encapsulation reduces the toxicity of the encapsulated drugs, minimizing side effects.
5. **Better Pharmacokinetics:** Liposomes provide improved pharmacokinetic profiles, including extended circulation times and reduced elimination, leading to more sustained drug delivery.
6. **Targeted Action:** Liposomes can be engineered to combine with specific ligands, allowing for active targeting to particular sites, further enhancing treatment precision.

Herbal Liposomal Formulation

Herbal liposomal formulations involve the encapsulation of herbal extracts or active plant compounds within liposomes, which are lipid-based vesicles. This method enhances the delivery and effectiveness of herbal medicines by improving their solubility, stability, and bioavailability. The liposomal structure allows for controlled and targeted release of the herbal components, potentially increasing their therapeutic efficacy.

These formulations can be tailored to encapsulate both lipophilic (fat-soluble) and hydrophilic (water-soluble) substances, depending on the properties of the herbal compounds. The use of liposomes in herbal medicine offers several advantages, such as better absorption, reduced toxicity, and the ability to protect sensitive herbal ingredients from degradation. Additionally, liposomal encapsulation can enhance the stability of the herbal compounds, allowing them to remain effective over longer periods.

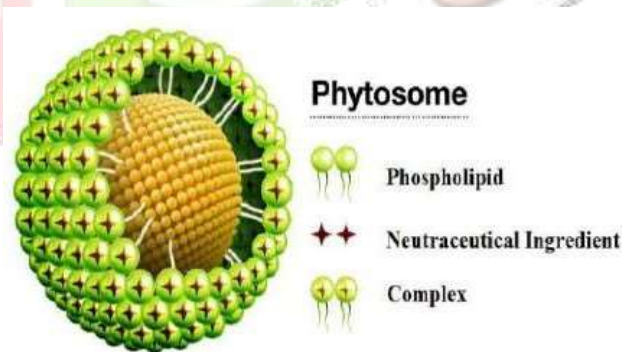
Herbal liposomal formulations are gaining popularity in the treatment of various conditions, including chronic diseases, cancer, and skin disorders, due to their ability to deliver plant-based medicines more efficiently and with fewer side effects.

PHYTOSOMES:

Phytosomes are advanced lipid-compatible complexes formed by combining water-soluble plant constituents, particularly polyphenolic compounds like flavonoids, with phospholipids. Many bioactive ingredients in herbal medicines, especially flavonoids, have poor oral bioavailability, which limits their effectiveness. Phytosomes improve the bioavailability of these compounds by enhancing their ability to pass through lipid-rich biomembranes more efficiently than conventional herbal extracts. This results in better absorption and, ultimately, greater delivery of the active ingredients into the bloodstream.

Initially developed for cosmetic applications, phytosomal complexes have recently shown significant potential in drug delivery, demonstrating promising results in areas such as cardiovascular health, anti-inflammatory treatment, liver protection, and cancer therapy. When compared to non-complexed herbal extracts, phytosome complexes exhibit superior pharmacokinetic and therapeutic profiles. .

Fig 2 : Structure of Phytosome



Advantages of Phytosomes

1. **Improved Bioavailability:** Phytosomes enhance the bioavailability of active ingredients through phospholipid complexes.
2. **Better Absorption:** They offer superior absorption in the gastrointestinal tract (GIT), ensuring more effective delivery of herbal compounds.
3. **Enhanced Treatment Outcomes:** The higher bioavailability contributes to better therapeutic results, making treatments more effective.

4. **Lower Dosage Requirements:** Due to increased bioavailability, smaller doses are sufficient for therapeutic benefits.
5. **Increased Stability:** Phytosomes provide greater stability for the active ingredients, preserving their effectiveness over time.
6. **Superior Penetration:** With excellent lipophilicity, phytosomes are often preferred over liposomes in cosmetics due to their superior ability to penetrate the skin.
7. **Therapeutic Benefits:** Phytosomes offer notable therapeutic effects, particularly in areas like liver protection and inflammation.
8. **Liver Protection:** Phosphatidylcholine in phytosomes not only acts as a carrier but also offers protective benefits for the liver.

Herbal Phytosomal Formulation

Active Ingredient	Biological Activity	Application of Liposomal Formulation
Quercetin	Antioxidant	Improves effectiveness of treatment
Oxymatrine	Anti-viral	Enhancement of bioavailability
Ginkgo biloba	Cardioprotective, anti-asthmatic	Induced therapeutic effect
Embelin	Antibacterial and anti-fertility	Increase in solubility

ETHOSOME:

Ethosomes are flexible, soft lipid vesicles composed mainly of water, ethanol (or isopropyl alcohol) in relatively high concentrations (20-45%), and phospholipids. Due to their high deformability, ethosomes possess unique characteristics that allow them to pass through human skin intact. The phospholipids used in ethosomal formulations, typically ranging from 0.5% to 10%, contribute to the vesicle structure and enhance the system's ability to deliver active ingredients effectively through the skin.

Phospholipids with varying chemical structures, such as phosphatidylcholine (PC), hydrogenated phosphatidylcholine, and phosphatidylethanolamine (PE), are commonly used in ethosomal formulations. Among the preferred options are soy-derived phospholipids like Lipoid S100 and Phospholipon 90 (PL-90).

The high alcohol content (20-45%) in ethosomes contributes to the vesicles' softness, flexibility, and stability. It also disrupts the skin's lipid bilayer, enhancing membrane permeability and facilitating deeper penetration. Commonly used alcohols include isopropyl alcohol and ethanol. Additionally, glycols such as propylene glycol and Transcutol are often incorporated as penetration enhancers. Cholesterol, typically added in concentrations ranging from 0.1% to 1%, can further improve the stability of ethosomal vesicles.

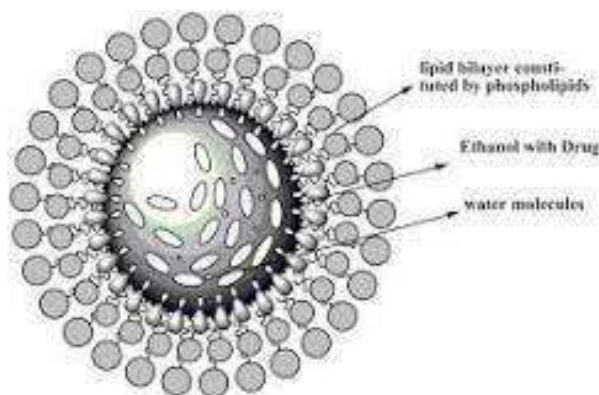


Fig 3 : Structure Of Etosomes

HERBAL ETHOSOMAL PREPARATION- [7]

Active Ingredient	Biological Activity	Application of Liposomal Formulation
Sophora Alopecuroides	Anti-endotoxic, anti-cancer	Ethosome enhances delivery of drugs through the stratum corneum barrier into the deep layer of the skin.
Matrine	Antibacterial, anti-inflammatory	Increase the per cutaneous permeation and improve anti-inflammatory effect

Advantages of Ethosomes

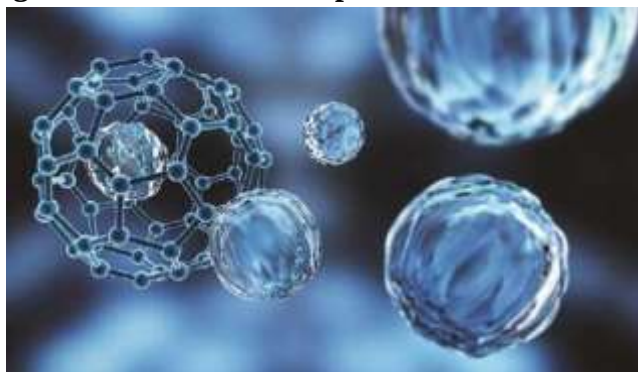
1. **Enhanced Skin Penetration:** Ethosomes improve the penetration of medications through the skin, making them ideal for transdermal drug delivery.
2. **Capability for Large Molecules:** This system can effectively deliver large molecules, including peptides and proteins.
3. **Safe Ingredients:** The formulation uses safe and biocompatible raw materials, reducing the risk of adverse effects.
4. **High Patient Compliance:** The ethosomal formulation is often delivered in a semisolid form (such as a gel or cream), which enhances patient compliance due to ease of application.
5. **Non-invasive and Convenient:** The ethosomal system is non-invasive, easy to commercialize, and offers a passive delivery mechanism.
6. **Wide Range of Applications:** Ethosomal drug delivery technology has broad applications across various industries, including pharmaceuticals, cosmetics, and veterinary care.

NANOPARTICLES:

Nanoparticles are solid particles, either amorphous or crystalline, typically ranging in size from 10 to 200 nm. These include nanospheres and nanocapsules, which are capable of encapsulating or adsorbing drugs, thereby protecting them from enzymatic and chemical degradation. In recent years, biodegradable polymeric nanoparticles have attracted significant interest as potential drug delivery systems due to their ability to enable controlled drug release, target specific tissues or organs, and serve as carriers for DNA, proteins, and peptides, including for gene therapy and oral drug delivery.

The advantages of using nanoparticles in drug delivery include enhanced absorption of the active ingredient, prolonged storage, improved solubility, reduced dosage requirements, and minimized side effects. For example, curcumin, an anticancer compound found in *Curcuma longa* rhizomes, has limited therapeutic effects due to its poor water solubility and low bioavailability. However, by utilizing crosslinked random copolymers of isopropylacrylamide, N-vinyl-2-pyrrolidone, and polyethylene glycol monoacrylate, curcumin nanoparticles have been developed to significantly improve its bioavailability and therapeutic potential.

Fig 4 : Structure Of Nanoparticles



Advantages of Nanoparticles

1. **Targeted Delivery:** Nanoparticulate technology ensures that herbal formulations are delivered directly to the site of action, enhancing treatment precision.
2. **Improved Solubility and Pharmacokinetics:** Encapsulating drugs within nanoparticles can enhance their solubility and improve their pharmacokinetic profile.
3. **Enhanced Bioavailability:** Nanoparticles can aid in penetrating various biological barriers, increasing the bioavailability of the drugs.
4. **Localized Treatment:** This technology allows for the direct delivery of medications to the affected area, minimizing systemic exposure and potential environmental damage.

HERBAL NANOPARTICULATE FORMULATION

Active Ingredient	Biological Activity	Application of Liposomal Formulation
Berberine	Anti-neoplastic activity	H. pylori growth inhibition
Hypocrellins	Antiviral activity	Improved performance in both stability and hydrophilicity
Silybin	Anti-hepatotoxic activity	Shows sustained release and targeting system

NIOSOMES:

Niosomes are microscopic, lamellar structures formed in aqueous environments using a nonionic surfactant, cholesterol, and a charge-inducing agent. The unique architecture of niosomes, with both hydrophobic and hydrophilic components, allows them to encapsulate a wide range of pharmacological substances. These vesicles have been studied for various medicinal applications, particularly for their ability to reduce systemic toxicity and prolong the release of therapeutic agents, thus minimizing the rate at which the body clears the drug.

Unlike liposomes, niosomes offer several advantages. They are more cost-effective and do not suffer from the chemical instability issues of liposomes, such as oxidative degradation of phospholipids. Niosomes also require less specific handling and storage, and they are less likely to experience the purity inconsistencies associated with natural phospholipids. As a result, niosomes are seen as a promising alternative to liposomes in drug delivery systems.

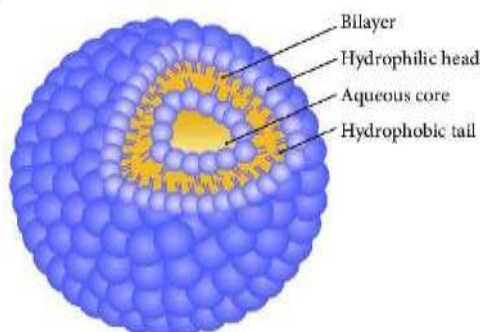


Fig 5 : Structure Of Niosomes

Advantages of Niosomes

1. Niosomes are stable and osmotically active.
2. They enhance the stability of encapsulated drugs.
3. Special handling or storage of surfactants is not required.
4. Niosomes can improve drug penetration for oral, parenteral, and topical applications.

MICROSPHERES:

. They are often described as "monolithic spheres" where therapeutic agents are evenly dispersed throughout a matrix of one or more miscible polymers. This distribution can occur on a macroscopic or molecular scale. Microspheres, also known as "microparticles," offer several advantages in drug delivery, such as improved patient compliance due to the need for fewer doses. The uniformity and sustained release properties of microspheres contribute to consistent therapeutic effects. Their unique morphology allows for controlled drug release and degradation, reducing side effects and enhancing the bioavailability of the drug.

MICROSPHERE HERBAL FORMULATION

Active Ingredient	Biological Activity	Application of Liposomal Formulation
Ginsenoside	Anti-cancer activity	To enhance solubility and stability
Quercetin	Antioxidant and anti-inflammatory	Enhancing its bioavailability and sustain release the formulation
Zedoary oil	Hepatoprotective	Sustained-release and higher bioavailability
Rutin	Cardiovascular and cerebrovascular	Targeting into cardiovascular and cerebrovascular regions

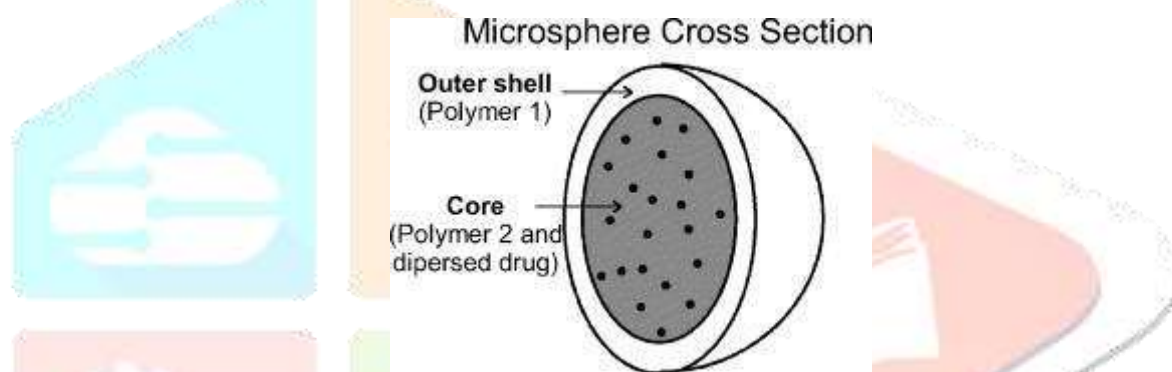


Fig 6 : Structure Of Microspheres

Advantages of Microspheres

Microspheres offer several benefits in pharmaceutical delivery systems. They can be administered via injection or oral ingestion, tailored to achieve specific drug release profiles, and used for targeted delivery to particular sites, including organ-specific release in certain cases. The drug is efficiently released from the microsphere matrix, ensuring effective therapeutic action.

MICROEMULSION:

These systems are used for various drug delivery methods, including transdermal, topical, ocular, percutaneous, oral, and parenteral routes, offering controlled or sustained release of the drug . The phase diagram is essential for characterizing microemulsions, and the pseudoternary phase diagram is commonly employed for their development. This method divides the diagram into distinct zones, including specific areas for microemulsion formation, with each component present in its pure form.

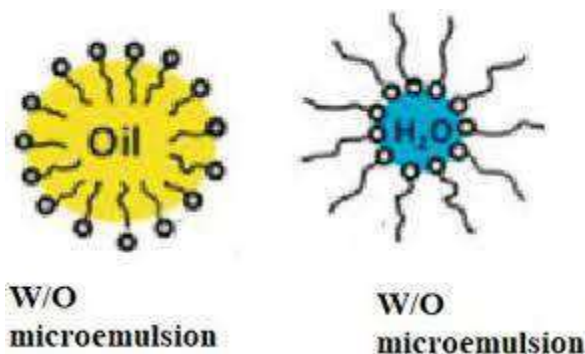


Fig 7: Structure Of Microemulsion

Advantages of Microemulsion

1. The absorption process reduces variability in drug delivery.
2. Lipophilic drugs are effectively solubilized.
3. Provides a solution for water-insoluble drugs.
4. Enhances bioavailability.
5. The product can be administered through various routes, including oral, intravenous, and topical.
6. The drug molecules penetrate quickly and efficiently.

Pharmaceutical Excipients

Excipients are integral components of a medication formulation, serving as a delivery system for the active pharmaceutical ingredients by providing the necessary vehicle. These materials serve as inert agents that help support and enhance the action of the active pharmaceutical ingredient (API). The term "excipient" is derived from the Latin word "excipere," meaning "to receive or accept." The quality of a pharmaceutical product is influenced by the production methods, the type of active ingredient, and the excipients used. Excipients play a crucial role in improving the performance of the API, ensuring the safety and effectiveness of the product.

Key Features of Excipients

- Protect and stabilize the formulation.
- Add bulk to the formulation for precise dosage.
- Enhance patient acceptance and compliance.
- Improve the bioavailability of the active ingredient.

Pharmaceutical Herbal Excipients

Pharmaceutical excipients are inactive substances used in combination with active ingredients to create medications. Plant-based excipients, including Agar, Alginate, Starch, Carrageenan, Guar Gum, Xanthan Gum, Gelatin, Pectin, Acacia, Tragacanth, and Cellulose, serve various purposes in the pharmaceutical industry. These excipients act as binders, disintegrants, protectants, thickening agents, bases for suppositories, gelling agents, stabilizers, and coating agents.

Advantages of Herbal Excipients

- Biodegradable
- Biocompatible and non-toxic
- Cost-effective
- Readily available

CONCLUSION:

Herbal remedies and plant-based compounds hold significant therapeutic potential that warrants further exploration using advanced drug delivery systems. This research highlights various types of herbal formulations, their compositions, applications, and innovative delivery methods, along with the current market landscape. To maximize the effectiveness of phytotherapeutics, a scientific approach is essential, one that ensures precise and unique delivery to enhance patient compliance and reduce the need for repeated dosages. The development of novel drug delivery systems (NDDS) for natural compounds offers a promising solution. These systems can enhance the bioavailability and therapeutic effects of herbal medicines, often improving their efficacy compared to traditional formulations. For instance, sublingual administration, which bypasses first-pass metabolism, offers a rapid onset of action due to the rich blood supply in the sublingual mucosa. Certain herbal ingredients, when integrated into novel delivery systems, have shown improved therapeutic outcomes at lower doses than traditional extracts. This presents substantial potential for advancing drug delivery technologies, particularly for high-cost herbal medicines.

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