A Review: Advanced Drug Delivery Technique

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DOI: https://doi.org/10.51584/IJRIAS.2025.100800030

Received: 09 August 2025; Accepted: 16 August 2025; Published: 01 September 2025

ABSTRACT

A novel drug delivery system represents an innovative method for administering drugs, addressing the shortcomings of traditional delivery approaches. In our country, the rich heritage of Ayurveda holds immense potential, which is only beginning to be fully appreciated in recent years. However, the conventional methods used to deliver herbal medicines often lead to diminished drug efficacy. Applying advanced drug delivery technologies to herbal medicine can enhance their effectiveness while minimizing side effects. This concept forms the foundation for integrating novel drug delivery methods with herbal treatments.

Integrating these systems with Indian Ayurvedic medicines is crucial for tackling more severe health conditions. Historically, herbal medicines were overlooked for novel formulation development due to a lack of scientific validation and challenges in processing, such as standardization, extraction, and identifying active components in complex polyherbal formulations. Nevertheless, contemporary phytopharmaceutical research can meet the scientific demands—like pharmacokinetics, mechanism of action, site-specific action, and precise dosing—necessary for incorporating herbal medicines into advanced delivery systems. These include nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, and solid lipid nanoparticles, among others. This article reviews various drug delivery technologies applicable to herbal actives, along with illustrative examples.

INTRODUCTION

In recent decades, significant focus has been placed on the development of novel drug delivery systems (NDDS) for herbal medicines. These advanced delivery systems are expected to meet two key criteria: first, they should release the drug at a rate that aligns with the body's therapeutic needs over the course of treatment; and second, they should effectively transport the active components of the herbal medicine to the specific site of action. Conventional dosage forms, including extended-release formulations, generally fail to meet these requirements.

In the field of phyto-formulation research, the creation of nano-based delivery systems—such as polymeric nanoparticles, nanocapsules, liposomes, solid lipid nanoparticles, phytosomes, and nanoemulsions—has shown several advantages for herbal medicines. These benefits include enhanced solubility and bioavailability, reduced toxicity, improved therapeutic efficacy, increased stability, targeted delivery to tissue macrophages, and sustained drug release.

Protection against physical and chemical degradation makes nano-sized novel drug delivery systems a promising approach for enhancing the effectiveness of herbal medications and addressing challenges commonly associated with plant-based medicines. Liposomes, which are biodegradable and generally non-toxic carriers, can encapsulate both water-soluble and fat-soluble substances

[1]. Liposome-based drug delivery systems offer the potential to improve the therapeutic index of anti-cancer agents by either increasing drug accumulation in tumor cells or reducing exposure in healthy tissues. This is achieved through the enhanced permeability and retention (EPR) effect, as well as through various targeting strategies

[2]. The key advantages of using liposomes include:

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VIII August 2025

i)high biocompatibility,

ii)ease of preparation,

iii) chemical versatility that allows for the incorporation of hydrophilic, amphiphilic, and lipophilic compounds, and

iv) the ability to tailor their pharmacokinetic properties by modifying the bilayer composition [3]. Delivery to the reticuloendothelial system (RES) is also efficiently accomplished, as conventional liposomes are typically sequestered by the RES

[1]. Innovative delivery strategies can further enhance the effectiveness of herbal cosmetic formulations on the skin

[4]. Similarly, other vesicular systems such as nanoemulsions, ethosomes, and transferosomes are highly effective and offer various advantages for delivering herbal medicines. Some of these benefits are discussed in this article.

The phytosome technique has been widely applied to a variety of popular herbal extracts such as *Ginkgo biloba*, grape seed, hawthorn, milk thistle, green tea, and ginseng. The flavonoids and terpenoids present in these herbal extracts are particularly well-suited for binding directly with phosphatidylcholine. Phytosomes are formed by linking individual active components from herbal extracts with phosphatidylcholine, resulting in a formulation that is better absorbed and therefore more effective than traditional herbal extracts. Research indicates that the absorption of silybin from a silybin-phytosome complex is approximately seven times greater than that from a standard milk thistle extract.

Drugs can also be embedded or dissolved in nanoparticles (NPs), or they can be adsorbed onto or conjugated with the surface of these particles. Encapsulating drugs in nanoparticles enhances their solubility and pharmacokinetic profile, and in some cases, may facilitate the continued clinical development of new chemical entities that would otherwise be hindered due to poor pharmacokinetic characteristics.

Nanoparticle carriers primarily consist of synthetic biodegradable polymers and natural polymers. Synthetic options typically include poly-α-cyanoacrylate alkyl esters, polyvinyl alcohol, polylactic acid, and polylactic-co-glycolic acid. Natural polymers are usually categorized into proteins (such as albumin, gelatin, and legumin) and polysaccharides (such as cellulose, starch and its derivatives, alginate, dextran, and chitosan).

This article aims to explore various aspects of the development of novel herbal formulations, including preparation methods, selection of active ingredients, release efficiency, and potential applications

Transferosomes

The term *transferosome* is a registered trademark of the German company IDEA AG, used to describe its proprietary drug delivery technology. Derived from the Latin *"transferre"* meaning “to carry across,” and the Greek *"soma"* meaning “body,” the name reflects the carrier’s function in transporting substances.

A transferosome is an artificially engineered vesicle designed to mimic natural cell vesicles or cells involved in exocytosis, making it well-suited for controlled and potentially targeted drug delivery. These nanocarriers show great promise for non-invasive transdermal drug administration.

Transferosomes are ultra-deformable vesicles consisting of an aqueous core surrounded by a flexible lipid bilayer. The interaction between their composition and structural shape enables them to self-optimize and self-propel. They can deliver both small and large molecular weight drugs across the skin.

Specially designed to be highly flexible, these lipid-based vesicular systems can penetrate the stratum corneum (outer skin layer) intact and act as carriers for targeted and sustained release of therapeutic agents. Their design

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VIII August 2025

allows them to easily accumulate in porous tissues like glandular structures, enabling effective peripheral targeting.

Moreover, transferosomes can function as drug depots, allowing for controlled and prolonged drug release. Their enhanced delivery efficiency is largely due to the diffusion gradient between the outer and inner layers of the skin, which facilitates penetration. This natural transdermal hydration gradient in the body aids in their movement through the intact skin.

Because of their remarkable flexibility, transferosomes are ideal for non-invasive delivery of a wide range of drugs, including those with small, medium, or large molecular sizes.

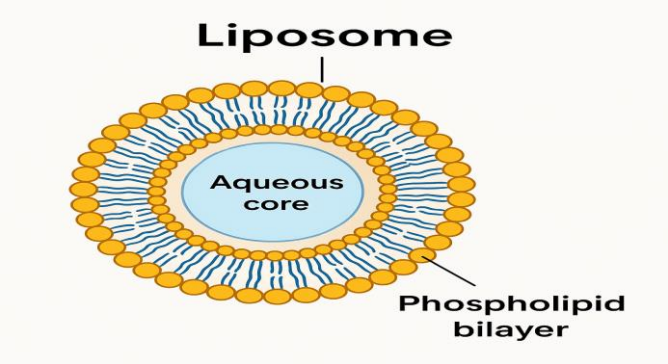
Liposome

Liposomes are nanoscale vesicles composed of organized lipid bilayers, featuring a hydrophobic exterior and a hydrophilic interior, typically ranging in size from 20 to 1000 nanometers. Their unique structural and compositional features lend them exceptional biocompatibility and biodegradability. As a result, liposomes can significantly improve the solubility of drugs and reduce their toxicity. They are versatile carriers capable of encapsulating both water-soluble and fat-soluble drugs, effectively shielding the active compounds from degradation while minimizing their accumulation in non-target organs and tissues

The integration of liposomal drug delivery systems into clinical use, a process that has taken nearly 50 years of research and development in nanotechnology, represents a major milestone in the advancement of treatments for cancer, bacterial infections, and vaccine delivery. For example, using solid lipid nanoparticles to deliver the anticancer compound resveratrol significantly increased its concentration in the brains of Wistar rats, compared to free resveratrol—demonstrating efficient brain tumor targeting and reduced systemic toxicity

In cancer treatment, liposome-based delivery of radiosensitizers enhances the precision and effectiveness of X-ray radiation on tumors. Zhao et al. developed a robust antigen-capturing stapled liposome (ACSL) with an active surface, which can collect and transport tumor-associated antigens (TAAs) from lysosomes to the cytoplasm of dendritic cells. This facilitates improved antigen cross-presentation and triggers a strong, T cell-mediated antitumor immune response and lasting immune memory following localized irradiation. Moreover, liposomal encapsulation of doxorubicin has been shown to reduce the drug's cardiotoxic effects and limit common side effects such as bone marrow suppression, hair loss, nausea, and vomiting. Other research has shown that decoquinate-loaded nanoliposomes (DQNLs), produced using thin-film dispersion and ultrasonic techniques, exhibit enhanced anticoccidial efficacy.

Lipid nanoparticles (LNPs) are a key innovation within liposome-based delivery systems and have significantly advanced the development of oligonucleotide-based therapies. Unlike traditional liposomes, LNPs lack hydrophilic cavities and are instead composed of cationic phospholipids combined with negatively charged nucleic acids through electrostatic interactions, forming multilayered cores surrounded by lipid layers. These structures protect the encapsulated oligonucleotides from enzymatic degradation during transport and enable efficient cellular delivery, where the therapeutic agents are released and expressed as functional proteins. Researchers at the University of Texas Southwestern Medical Center have introduced a novel approach known as Selective Organ Targeting (SORT), which enhances the precision of LNP delivery to specific organs.

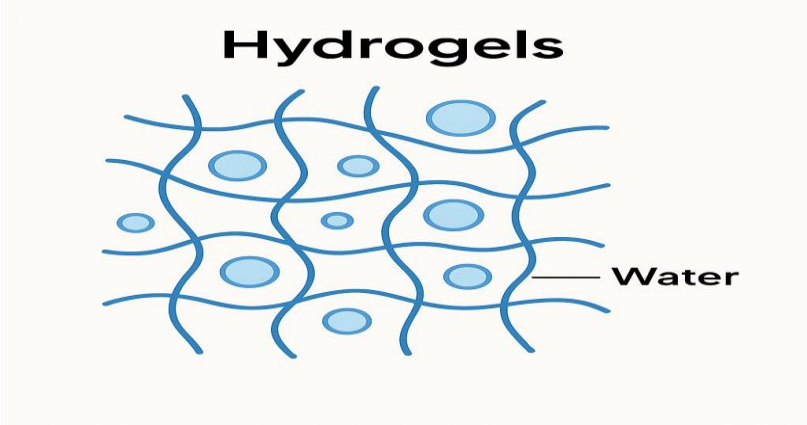


ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VIII August 2025

Hydrogels

Hydrogels, which are polymer networks formed through either physical or chemical crosslinking, have the distinct capability to absorb water and interact with specific organic solvents. These hydrogel-based nanodrug delivery systems offer outstanding biocompatibility, biodegradability, and minimal toxicity, enabling the controlled and sustained release of therapeutic agents.

In tumor treatment, the immune response triggered by radiation therapy alone is often inadequate, making it necessary to incorporate immune adjuvants to enhance the function of antigen-presenting cells. To address this, Wang et al. developed a near-infrared light-activated hydrogel nanomotor that can penetrate tumor tissues and release drugs directly within cells. This system improves immune system activation and combines phototherapy, chemotherapy, and immunotherapy for a synergistic treatment effect. Hydrogels also serve as excellent materials for tissue regeneration. For example, created an anti-swelling nanofiber hydrogel with superior biocompatibility and biodegradability, which supports fibroblast movement and promotes new blood vessel formation during wound healing. Similarly, introduced a novel hydrogel nanodrug delivery platform that carries ligands designed to competitively bind ATP released by tumor cells following oxaliplatin or X-ray treatment. This binding triggers the release of immune adjuvants, further enhancing the combined therapeutic effect.



Tocosome

Tocosomes are advanced colloidal and vesicular systems designed to deliver bioactive agents. Their primary component is alpha-tocopherol phosphate (TP), a vitamin E derivative. Among the eight naturally occurring forms of vitamin E, alpha-tocopherol is the most dominant and biologically potent. TP is notable for its uniform particle size, high encapsulation efficiency, low immunogenicity, superior biocompatibility, and improved dissolution and permeability, all contributing to its extended stability [34]. These diverse features make Tocophersolan a versatile material for formulating drug delivery systems. Structurally similar to liposomes, tocosomes are made of amphiphilic compounds that form bilayer colloidal assemblies, behaving similarly in terms of drug delivery and release, despite their distinct chemical structures.

Clinical studies have highlighted TP's numerous health benefits, including its contributions to preventing atherosclerosis, protecting the cardiovascular system, reducing inflammation, and hindering the spread of tumors. TP-based formulations often incorporate combinations of phospholipids and cholesterol, which have been effectively applied for the encapsulation and controlled release of anticancer drugs such as 5-fluorouracil.

Sunitinib malate and sorafenib tosylate are two targeted treatments used against metastatic kidney cancer, each acting through different pathways to suppress angiogenesis and tumor growth. In an innovative study, Fariba and colleagues developed a coated tocosome by combining chitosan (CS) with poly(N-isopropylacrylamide) (PNIPAAm) using the Mozafari technique. This thermoresponsive nanocarrier shows improved stability, optimal particle size, and scalability, marking it as a promising platform for delivering sunitinib malate and sorafenib tosylate in cancer therapy.

Tocophersolan (TPGS), a synthetic, multifunctional polymer derived from vitamin E, is FDA-approved as a safe pharmaceutical excipient. Taxol and docetaxel (DTX), two powerful and low-toxicity natural anticancer agents,

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VIII August 2025

are widely employed in treating cancers such as ovarian, breast, and lung cancer. They work by promoting microtubule formation and inhibiting their breakdown, thereby blocking cancer cell division.TPGS was chemically modified with cholesterol to produce TPGS-CHMC, a novel delivery material with a reduced critical micelle concentration (CMC). TPGS-CHMC was shown to decrease mitochondrial membrane potential and cell membrane fluidity in paclitaxel-resistant ovarian cancer cells (A2780/T). When tested in A2780/T tumor-bearing nude mice, TPGS-CHMC/DTX micelles demonstrated significantly enhanced antitumor activity and lower toxicity compared to free DTX formulations.

Dendrimers

Dendrimers are nanoscale, radially symmetrical molecules with a precisely structured, uniform, and monodisperse architecture composed of branched, tree-like arms. These highly branched macromolecules were first discovered by Fritz Vögtle in 1978 and independently developed in the early 1980s by Donald Tomalia and his team, as well as George R. Newkome. The latter group referred to these synthesized macromolecules as "arborols," derived from the Latin word for trees. Although dendrimers are sometimes called “cascade molecules,” the term “dendrimers” is more widely accepted.

These nearly monodisperse macromolecules are made up of symmetrically branched units organized around a small core molecule or a linear compound. It is important to note that "dendrimer" represents a structural motif rather than a specific compound. Polyionic dendrimers lack a fixed shape and may change in size, conformation, and flexibility as the generation number increases.

Dendrimers feature a precisely engineered structure with terminal groups at the outer edges that can be chemically modified, allowing adjustments to their physical or biological properties. Their unique architecture makes dendrimers highly valuable in supramolecular chemistry, especially in host-guest interactions and self-assembly mechanisms. They are well-defined synthetic macromolecules, combining a large number of functional groups with a compact, dense structure.

Due to these characteristics, dendrimers have attracted significant attention for their potential applications, particularly in cancer therapy and diagnostic imaging. Their predictable and tunable properties make them an emerging class of nanoscale drug delivery platforms. As the generation of dendrimers increases, they tend to expand in diameter and adopt a more spherical shape.

Basic Structure of a Dendrimer:

1. **Core:**
    - The central part of the dendrimer.
    - Typically a single atom or a small molecule.
    - Serves as the origin from which the dendrimer grows.
2. **Branches (Interior Layers):**
    - Repeating units that emanate from the core in a symmetrical fashion.
    - Each branching layer is called a **generation** (G1, G2, G3, etc.).
    - As generations increase, the size and complexity of the dendrimer grow exponentially.
3. **Terminal Groups (Surface):**
    - The outermost functional groups attached to the final generation.

- These groups can be chemically modified to alter the dendrimer's solubility, reactivity, or biological activity.

Ethosomes are ethanolic liposomes and can be described as non-invasive drug delivery systems designed to transport therapeutic agents deep into the skin or into systemic circulation. These soft, flexible vesicles are optimized to enhance the penetration of active substances. Vesicles have long been recognized for their role in cellular communication and particle transport. They can also regulate drug release over time, protecting the drug from immune system responses or other elimination mechanisms, thereby enabling controlled and sustained release at a consistent concentration. A significant development in vesicle research was the discovery of a specialized type known as **ethosomes**. These are a modified form of conventional liposomal drug carriers. Ethosomes are lipid vesicles composed of phospholipids, a high concentration of ethanol or isopropyl alcohol, and water. Their size can range from a few nanometers to several microns. Ethosomes are particularly effective in penetrating skin layers more efficiently and achieving higher transdermal drug flux compared to traditional delivery systems.

CONCLUSION

Herbal medicines hold significant therapeutic potential, which can be better utilized through advanced drug delivery systems. However, factors like poor solubility in biological fluids and large molecular size often limit the ability of drug molecules to cross biological membranes, thereby affecting consistent absorption when administered orally or topically. Many plant extracts and phytochemicals, although highly effective in vitro, often fail to demonstrate the same efficacy in vivo due to these limitations—resulting in low absorption and poor bioavailability.

Standardized plant extracts or predominantly polar phytoconstituents such as flavonoids, terpenoids, tannins, and xanthones have shown improved absorption profiles when delivered through novel drug delivery systems (NDDS). These systems enhance their ability to cross biological membranes, leading to increased bioavailability. Consequently, a greater amount of the active compound reaches the target site (such as the liver, brain, heart, or kidneys), often at lower or similar doses compared to traditional extracts or isolated phytomolecules.

As a result, the therapeutic effect becomes more pronounced, prolonged, and detectable. Several promising phytoconstituents have already been effectively delivered using NDDS. Therefore, there is substantial potential in developing novel drug delivery systems to maximize the benefits of plant-based actives and extracts.

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ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VIII August 2025

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