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Review Article

Development of Novel Carrier System: A Key Approach to Enhance Bioavailability of Herbal Medicines

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ABSTRACT

Medicinal herbs have been utilised for thousands of years to cure various medical conditions. Medicinal herbs continue to play a significant role in the health care systems of a significant portion of the global population, particularly in developing nations. However, water soluble phytoconstituents (such as flavonoids, tannins and terpenoids) are poorly absorbed via passive diffusion or because of their poor lipid solubility and consequently demonstrating poor bioavailability. The majorities of physiologically active constituents are polar or water-soluble molecules. Herbal medications are beneficial when used properly, but they can be challenging to recognize, extract from and administer; as a result, adjustments are required to address these issues. The novel formulations of plant actives and extracts are reported to have notable benefits over traditional formulations. These benefits include increased solubility, bioavailability and toxicity protection; improved pharmacological activity; enhanced stability; improved tissue macrophage distribution; sustained delivery; and protection against physical and chemical degradation. NDDS encompasses a range of innovative delivery systems, including solid-lipid nanoparticles, transferosomes, phytosomes, microspheres, microemulsions and ethosomes. This review's goal is to provide an overview of several NDDS for the delivery of herbal medications.

Keywords: Phytosomes, Pharmacokinetics, Nanoparticles, Microspheres, Microemulsions.

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INTRODUCTION

The evolution of human civilization has been greatly aided by medicinal plants. Medicinal plants have long been considered the foremost source of medicine in almost all cultures and civilizations. Many contemporary medications are derived from medicinal plants, which are regarded as valuable resources for traditional medicine. Medicinal herbs have been used for thousands of years to cure illnesses, taste food, preserve it and stop disease outbreaks. The biological traits of plant species used worldwide are typically attributed to the secondary metabolites produced by the plants. Plant-derived compounds regulate microbial growth under a variety of situations.[1]

Throughout history, humans have relied on nature to provide them with basic needs such as food, shelter, flavours, scents, clothes, fertilisers, medicines and vehicles. In the healthcare systems of many parts of the world's population, medicinal plants continue to play a significant role. This is particularly true in poorer nations where herbal medicine has a long and continuous history of use. Both in industrialised and developing nations, there is a growing acknowledgement of the therapeutic and economic benefits of these plants.[2]

Given that nature has a vast chemical library, the practice of preparing medicines from herbs and plant extracts dates back thousands of years, with roots in ancient Egypt and China. The world's population now relies about 80% on plant-derived products and herbal remedies, which has reversed previous patterns. All forms of preparations made from herbs, spices, stems, leaves and other naturally occurring non-botanical materials are referred to as herbal medicines, phytomedicines, or herbal goods. They can be applied topically as prescription, over-the-counter, or even as makeup.[3]

Future Scenario of Medicinal Plants

Recently, advancements in the delivery of herbal drugs have been made with the goal of effectively managing human ailments. Every country looks for health care that goes beyond the conventional confines of contemporary medicine and many resort to herbal medicines for self-medication[4,5] Since there are roughly 500,000 plants in the world, there is a bright future for medicinal plants. The majority of these plants have not yet been studied for

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their potential medical benefits, which could be decisive in the handling of current and future research project.[6]

Emerging Need of Herbal Products Over Synthetic Medicines

The safety and efficacy of phytopharmaceuticals are not guaranteed by a universal regulatory framework in the majority of nations. It is rare to find evidence-based confirmation of the effectiveness of herbal medicines. On the other hand, information regarding the assessment of the toxicological and therapeutic effects of herbal medicines has just been accessible. Since the process of finding and developing new, safe medications is too drawn out, complex and costly, the pharmaceutical industry's research and development department invests billions of dollars on it. There is little to no information available about the biological destiny and disposition of the majority of herbal treatments utilised in conventional and ethnomedical practices. Because of the diversity of components, the difficulty in identifying biological or bioactive indicators and the lack of understanding regarding the agents' and their metabolites' fate *in vivo*, it might be difficult to determine the pharmacokinetics profile of natural medicines.[7]

Need of Development of Novel Carrier System

A herbal medicine's complex structure is made up of numerous active ingredients, each of which contributes to its therapeutic effectiveness and acts in concert with the others. When incorporated into innovative procedures, constituents like flavonoids, tannins and terpenoides demonstrate enhanced bioavailability and focused activity at low therapeutic doses. Traditional herbal formulations are effective, but the drug delivery method lacks standardisation, scientific support and the ability to identify individual chemical constituents in complicated polyherbal formulations. As a result, a novel carrier-based approach for herbals needs to be developed.

Herbal Novel Drug Delivery Systems

In order to achieve the desired distribution rate, innovative drug delivery technologies either incorporate the drug into the carrier system or alter the drug's molecular structure. Novel concepts were developed for managing the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, misrecognition and effectiveness of pharmaceuticals. These innovative techniques, which are based on an interdisciplinary approach combining molecular biology, pharmaceutics, polymer science and bio conjugate chemistry, are frequently referred to as NDDS. Various types of NDDS to deliver the herbal drug is given in Figure 1. The distribution of an effective level of the therapeutically active component is a prerequisite for the effectiveness of any herbal medicine. However, their bioavailability when applied topically or taken orally has a serious constraint.

Herbal medications are safe to use, but they can be challenging to prepare, recognize, extract and administer. To address these issues, new drug delivery systems, or NDDSs, have been developed. When compared to traditional cancer treatment techniques, NDDS is also advantageous. The herbal medications have been altered to improve their therapeutic value, lower their toxicity, produce a controlled and sustained release, promote patient compliance and improve their solubility and bioavailability. Liposomes, phytosomes, microspheres, microemulsions, transferosomes, ethosomes and solid-lipid nanoparticles are a few examples of the innovative carriers included in NDDS. This review's objective is to describe various HNDDS for the delivery of herbal medications.[8]

Improved tissue macrophage distribution, sustained delivery, protection against physical and chemical degradation, enhanced pharmacological activity, enhanced stability, enhanced solubility, bioavailability and protection from toxicity are just a few of the notable benefits of the novel formulations over traditional plant actives and extracts.[9,10]

Polar or water-soluble molecules make up the majority of the physiologically active components found in plants. Phytoconstituents that are soluble in water, such as tannins, terpenoids and flavonoids, are not well absorbed because of their large molecular size, which prevents them from being absorbed through passive diffusion, or because of their poor lipid solubility, which severely restricts their ability to cross biological membranes that are rich in lipids. This leads to poor bioavailability.[11] The classes in the biopharmaceutical classification system that these kinds of medications fall into are high solubility/low permeability (BCS Class III). The bioavailability of these extracts and each of their constituents has been found to be significantly increased by complexation with a few other clinically beneficial nutrients. Phospholipids are among the nutrients that are particularly useful for improving absorption.[12,13] Several researchers are working to develop novel drug delivery systems using herbs, such as mouth-dispersing tablets, sustained and extended release formulations, mucoadhesive systems, transdermal dosage forms, microparticles, microcapsules, nanoparticles, implants, etc., because they have a lot of potential. Certain ones have reached the benchmark, while others are still in the laboratory.[14]

Carrier Based Drug Delivery System

Since the features of the carrier determine the destination and fate of the drug entrapped in it, as long as the drug leaches from the system at a properly controlled rate, the use of carriers to target medications to different organs is based on this principle.[15]

Liposomes

Polar lipids, which are composed of hydrophilic and lipophilic groups of related molecules, are used to construct liposomes. This spherical, colloidal vesicle entraps an aqueous core containing medicine to improve the product's solubility, bioavailability and site of action targeting, among other aspects of its extended

release.[16] Nowadays, liposomal technology is the basis for many herbal formulations. However, there is still room for improvement because of the main drawbacks of this approach, which include low encapsulation, low efficiency and quick drug leakage when blood is present and inadequate storage facilities.[17] Various examples of liposomal herbal formulation enlisted in Table 1.

Phytosomes

Since ancient times, phytoactive ingredients have been used as medications; however, due to significant obstacles such as poor lipid solubility, high molecular size and breakdown in the stomach environment, their use is restricted. The phospholipid-complex approach has shown promise in recent times in overcoming these obstacles, either by improving the solubilizing or potentiating ability to cross the bio membranes and preventing the degradation of the active herbal ingredients. “Plants are referred to as "phyto," and "some" denotes a covering for a structure. One or two moles of polyphenolic phytoconstituents and phospholipid are typically reacted to create a phytosome. Either a 1:1 or 1:2 ratios could apply. In order to increase the bioavailability of active herbal components, researchers can use this phospholipid complex approach to transfer the constituents into systemic circulation by using some standard dosage forms, such as tablets and capsules.[18,19] The technique of creating phytosomes involves binding a standardised plant extract or any of its elements to phospholipids, primarily phosphatidylcholine, to form a lipid-compatible molecular complex. The pharmacokinetic and pharmacodynamic profiles of phytosomes are superior than those of traditional herbal extracts.[20] Various examples of phytosomal herbal formulation enlisted in Table 2. Hesperetin and hydrogenated phosphatidylcholine were combined and complexed to create a new hesperetin. Researched its pharmacokinetic properties in rats intoxicated with $CC1_4$ as well as its antioxidant activities. The phytosome exhibited strong antioxidant activity, according to the study's findings. Research on pharmacokinetics has demonstrated that phytosomes had higher bioavailability at the same dosage than the parent molecule.[21,22] Structural differences between phytosomes and liposomes are given in Figure 2.

Nanoparticles

These colloidal particle systems, which have sizes below microns, serve as medicine molecule carriers. Applications of nanoparticles in medicine include the management of cancer, reticulo-endothelial system infections and liver enzyme replacement therapy. The mean particle size of medication in this system is as small as 100 nm. Size reduction increases compound solubility, lowers dosage requirements and speeds up the pace at which herbal drugs are absorbed.[30] At thenanoscale (1-100 nm), science, engineering and technology are combined to form nanotechnology. Because of their non-specific mode of action and poorly designed dose forms, conventional medications have certain side effects. One notable example of a novel drug delivery technology is nanoparticles. Innovative formulations of nanoparticles, such as liposomes, solid-lipid nanoparticles, microemulsions, ethosomes and polymeric nanoparticles with herbal molecules, can help deliver herbal medicines more effectively and selectively. They can also increase the drug's bioavailability at the target site, reducing the need for frequent dosing and, consequently, healthcare costs.[31]

Various examples of nanoparticle herbal formulation enlisted in Table 3.

Monoclonal Antibodies

These proteins are synthetic and only show selectivity towards a particular antigen. Cancer treatment is the main therapeutic use case being researched for monoclonal antibodies.

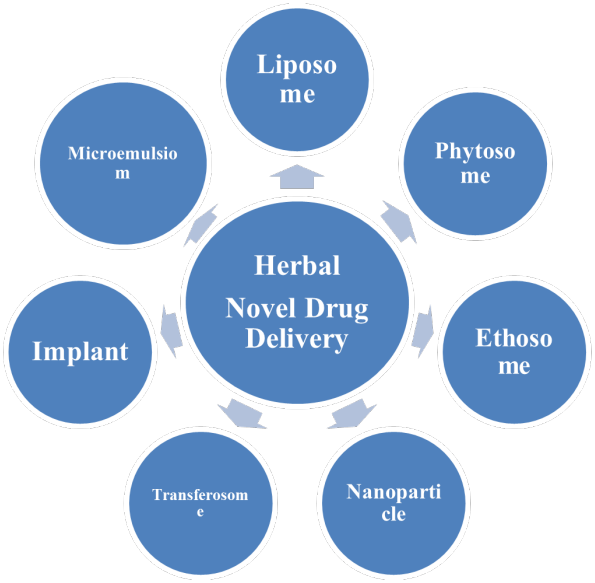

Figure 1: Different Herbal Novel Drug Delivery System.

Table 1: Liposomal herbal formulation.[23-26]

Formulations	Active ingredients	Applications of liposomes formulations	Biological activity	Method of preparation	% Entrapment efficiency	Route of administration
Quercetin liposomes	Quercetin	Reduced dose and enhanced penetration in BBB.	Antioxidant and Anticancer.	Reverse evaporation Technique.	60%	Intranasal
Encapsulated silymarin Liposome	silymarin	Improve bioavailability.	Hepatoprotective.	Reverse evaporation Technique.	69%	Buccal
Artemisia arboresence Liposome	Artemisia arboresence essential oil	Enhance penetration in cytoplasmic barrier.	Antimalarial	Film method and sonication.	60-74%	*In vitro*
Ampelopsin liposome	Ampelopsin	Increase efficiency.	Anticancer	Film-ultrasound Method.	62-3%	*In vitro*
Paclitaxel liposome	Paclitaxel	High entrapment efficiency and pH sensitive.	Anticancer	Thin film hydration method.	94%	*In vitro*
Curcumin liposome	Curcumin	Long circulating and high entrapment efficiency.	Anticancer	Ethanol injection Method.	88%	*In vitro*
Garlicin liposomes	Garlicin	Increase efficiency	Antioxidant for lungs.	Reverse phase evaporation method.	90%	-
Formulations	Active ingredients	Applications of liposomes formulations.	Biological Activity.	Method of Preparation.	% Entrapment efficiency	Route of administration
Flavanoids liposomes	Quercetin and rutin	Enhanced binding of flavonoids with Hb.	Antioxidant for Hb.	Solvent evaporation method.	-	*In vitro*
Usnea acid liposomes	Usnea acid	Increased solubility and localization.	Antimcrobial	Hydration of a thin lipid film with sonication.	99.5%	*In vitro*
Wogonin liposomes	Wogonin	Sustained release effect.	Anticancer	Film dispersion	81%	*In vivo*
Colchicine liposomes	Colchicine	Enhance skin accumulation and prolong release.	Antigout	Rotary evaporation sonication method.	66%	Topical
Catechins liposomes	Catechins	Increase permeation through skin.	Antioxidant and chemoprotective.	Rotary evaporation sonication method.	93%	Transdermal
Breviscapine liposomes	Breviscapine	Sustain delivery	CVS diseases	Double emulsification method.	87.9%	Intramuscular

Emulsion

Emulsions are biphasic systems in which the liquid or oil phase is always mixed with the water phase, which mixes instantly. They are harmless and non-irritating by nature and because of their larger surface area; they can pass through skin due to high skin permeability, which results in high bioavailability. 2 of this drug delivery device's main limitations are its non-emulsion compound's palatability and compatibility with other excipients. The sub-micro emulsion is referred to as a lipid emulsion, while the sub-microemulsion is called a nanoemulsion. These fine particles homogeneous dispersion and smaller size improved

Table 2: Phytosomal herbal formulation.[27-29]

Biological source	Chemical Classification	Advantages	Uses	Active ingredients
Silibiummarianm	Flavonoids	Increase in Absorption.	Hepatoprotective, Antioxidant.	Silybin
Vitis vinifera	Proanthocyandinis	Increase in antioxidant property	Antioxidant and Anticancer.	Catechin, epicatechin.
Curcuma longa	Polyphenols	Increase in Bioavailability.	Antioxidant, anti-inflammatory and Anticancer.	Curcumin, demethoxycurcumin and bis demethoxycurcumin.
Thea sinensis	Polyphenols, Flavon-3-ol	Increase in Bioavailability.	Antioxidant, neuro-protective and anticancer.	Epigallocatechin-3-gallate, epigallocatechin, Epicatechin-3-gallate, Epicatechin.
Panax ginseng	Saponin glycosides	Inhibit lipid Peroxidation.	Immunomodulator	Ginseng
Ginko biloba	Terpenoids	Improve bioavailability.	In cerebral Insufficiency.	Ginkoflavoneglucoside, ginkgolides, ginkgoic acids and Bilobalide.

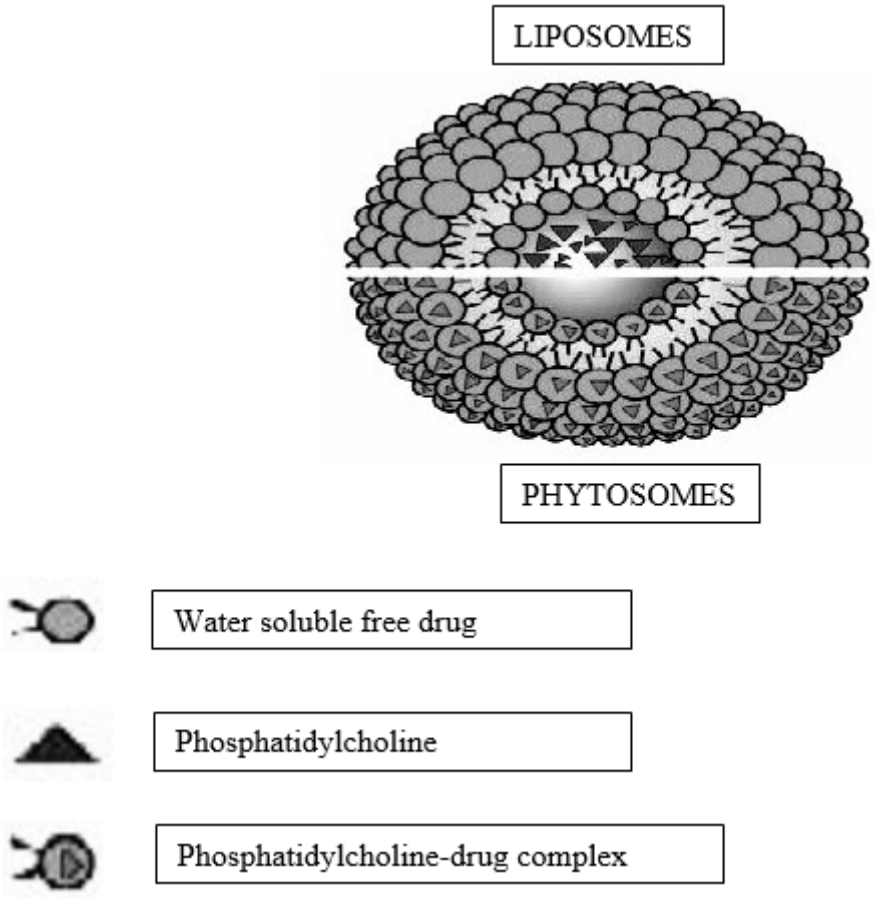

Figure 2: Showing structural differences between Phytosome and Liposome.

Table 3: Nanoparticle herbal formulations.[32,33]

Biological source	Chemical Classification	Advantages	Uses	Active ingredients
Cuscuta chinensis	Flavonolignans	Improve water Solubility.	Anticancer, immunostimulatory and Antihepatotoxic.	Ethanolic extract
Glycyrrhiza glabra	Saponin glycosides.	Saponin glycosides	Anti-inflammatory, antiviral and Antihepatotoxic.	Glycyrrhizic acid
Tripterygium wilfordii	Diterpene oxide	Increase solubility and decreases toxicity.	Anticancer and anti-Inflammatory.	Triptolide
Ginkgo biloba	Flavonoids	Increase cerebral blood flow.	Brain function Activation.	Extract of *ginkgo biloba*
Naringenin	Flavonoids	Increase solubility	Hepatoprotective	-
Artemisia annua	Alkaloids	Increase therapeutic index	Anticancer	Paclitaxel
Berberis vulgaris	Isoqulinoline	Sustained drug Release.	Anticancer	Berberine
Comptotheca acuminata	Qulinoline	Increase solubility	Anticancer	Hydroxycamphtothecin

their effectiveness. In addition to being more economically viable and less harmful than synthetic pesticides, the nano emulsion can be utilised as an option for the management of vector-borne diseases.[34] Various examples of emulsion herbal formulation enlisted in Table 4.

Microspheres

Another name for it is a micro particle. The diameter of spherical particles in a microsphere ranges from 1 µm to 1000 µm. Every drug particle is scattered within its own particle. It is produced using a variety of materials. To create microparticles, a variety of plant active ingredients, such as rutin and zedoras extract, have been utilised. Recent researches on non-biodegradable microspheres state. The only polymer that has been approved for human usage is polylactic acid. While hollow microspheres are utilised as additives to reduce the density of material, solid and heavy microspheres are employed for distinct purposes. They can be administered intravenously or eaten. It can be applied to drug delivery that is site-specific. The active ingredient in turmeric is curcumin, which was extracted from Curcuma longa. Using the emulsion solvent diffusion approach, curcumin floating microspheres were effectively created. The microspheres demonstrated high drug entrapment efficiency and a good yield. Microspheres flow characteristics fell within the permissible range, making it simple to fill capsules with them. The formulations show potential for further development into drug delivery systems for oral administration of curcumin, as the release properties were found to be satisfactory.[35] Various examples of microsphere herbal formulation enlisted in Table 5.

Ethosomes

Phospholipid mixtures and high ethanol concentrations combine to form ethosomes. This carrier has a deep skin penetration rate, which enhances drug delivery to the skin's deeper layers and blood circulation. These formulations work well for the topical administration of alkaloids to patients comfort in the form of gel and cream. By fluidizing the skins lipid domain, they exhibit an increase in permeability through the skin. The limits of Ethosomes' topical delivery system are its unstable nature and low skin penetration.[40] Various examples of ethosomal herbal formulation enlisted in Table 6.

Trans-Dermal Drug Delivery

A patch that is affixed to the body's surface is used for trans-dermal medication delivery. The purpose of this medicated adhesive patch is to deliver the active ingredient gradually over a period of several hours to days following skin application. Diffusion through multiple skin layers, the medication in the transdermal patch enters the systemic circulation and eventually reaches the affected organ. With this technique, drugs are delivered at a controlled rate with great bioavailability, ease of application and long-lasting effects. The maintenance of a constant drug

Table 4: Emulsion herbal formulation.[36,37]

Biological source	Category	Application	Uses	Active ingredients
Silybum marianum	Antioxidant	Increase in solubility and therapeutic activity.	Hepato-protective	Silymarin
Berberis vulgaris	Anti-arrythemic	Improve residence time and absorption.	Anticancer	Berberine
Sophora alopecuerides	Anti-cancer	Increase in percutaneous permeability.	Anti-bacterial, Anti-inflammatory, Anti-virus.	Matrine
Curcuma zedooria	Hepatoprotective	Improved aqueous dispersibility, stability and oral bioavailability.	Hepato-protection, Anticancer and anti-Bacterial.	β-elemene
Ubiquinone	Antioxidant	Enhancement in solubility, bioavailability.	Antioxidant	–
Colchicum autumnale	Anti-inflammatory	Improved oral bioavailability.	Treatment of gout.	Colchicine
Genista tinctoria	Anti-gout	Improved skin Permeation.	Anticancer	Genistein

Table 5: Microsphere herbal formulations.[38,39]

Formulations	Active ingredients	Advantages	Uses	Method of preparation	Size in µm	Route of Administration
Rutin-alginate-chitosan microcapsules	Rutin	Targeting into cardiovascular and cerebrovascular region.	Cardiovascular and cerebrovascular diseases.	Complex-coacervation Method.	165-195	*In vitro*
Zedoary oil microsphere	Zedoary oil	Sustained release and Higher bioavailability.	Hepato-protective.	Quasi-emulsion-solvent diffusionMethod.	100-600	Oral
CPT loaded microspheres	Camptothecin	Prolonged-release of camptothecin.	Anticancer	Oil-in-water evaporationMethod.	10	Intra-peritoneal
Quercetin microspheres	Quercetin	Significant decrease in the dose size.	Anticancer	Solvent evaporative.	6	*In vitro*
Cynara scolymus microspheres	*Cynara scolymus* extract.	Controlled release of nutraceuticals.	Nutritional supplement	Spray-drying technique	6-7	Oral

plasma level and hepatic first pass metabolism are limitations.[41] *Momordica charantia* is typically taken as a diabetic medication. The transdermal film was made by employing hydroxyl propyl methyl cellulose as a polymer to create the fractionated component from the ethanolic extract of *M. chirantia* fruits. Acute and sub-acute anti-hyperglycemic activity in diabetic rats, as well as folding durability, thickness, weight variation, drug contents and *in vitro* diffusion studies were assessed for the films. The percentage release of active constituents from *M. charantia* transdermal patches (2 cm^2; 10 mg/patch) was found to be satisfactory. With the use of contemporary pharmaceutical formulation processes, it has been discovered that the transdermal approach causes very little skin irritation and *in vivo* data show that the patches efficiently lower blood glucose levels.[42]

Transferosomes

Highly deformable vesicles, or transfersomes, have emerged as a potential medicine carrier that can transport big molecules through intact mammalian skin. Transfersomes have a high degree of deformability, which facilitates their rapid passage across the subcutaneous tissue's intercellular lipid rout. Various examples of transferosomal herbal formulation enlisted in Table 7.

Table 6: Ethosomal herbal formulation.[43]

Biological Source	Category	Application	Use	Active ingredient
Glycyrrhiza glabra	Triterpenoid saponins glycoside.	Improved Anti-inflammatory activity and sustained release Action.	Treatment of dermatitis, eczema and psoriasis.	Ammonium glycyrrhizinate
Cannabis sativa	Renin	Improved patient compliance and increased skin Permeation.	Treatment of Rheumatoid arthritis.	Tetrahydrocannabinol (THC).
Tripteygium wilfordii Sophora alopecuerides	Quinazoline alkaloid	Increased percutaneous permeability Increased permeability.	Anti-inflammatory, Anti-tumor, Anticancer, Antiendotoxic.	Triptolide Matrine, Oxymatrine, Sophoridine, Sophocarpine (Alkaloid extract).

Table 7: Transferosomes herbal formulations.[44,45]

Biological Source	Category	Application	Use	Active Ingredients
Capsicum annum	Resins	Increased skin penetration.	Treatment of Rheumatism	Capsaicin
Curcuma longa	Resins	Increase skin permeability.	Anti-inflammatory	Curcumin
Catharanthus roseus	Indole alkaloid	Increase in permeability.	Anticancer	Vincristine
Colchicum automnale	Amino alkaloid	Reduction in GIT effects.	Treatment of Gout	Colchicine

Micro Pellets

The agglomeration process known as "micro pellets" breaks down fine powder or granules of bulk medications and excipients into tiny, freely flowing, semi-spherical units. Pellets include many particles. Systems are used interchangeably because they offer both medicinal and technological benefits over single unit dose forms. For instance, phyto-granules, or active herbal compounds, are found in herb micropellets. *Andrographis penniculata* extract was encased in calcium alginate microparticles. Rat hepatoprotective response to paracetamol-induced hepatotoxicity was assessed using these pellets. By lowering AST, ALT and liver weight, the bitter alginate microparticles containing the alcoholic extract of *Andrographis penniculata* were found to positively reduce the hepatotoxicity caused by paracetamol.[46]

Polymeric Micelle Formulation

These are made of amphiphillic blocks and have been effectively utilised to deliver drugs that are insoluble in water. By modifying the physicochemical characteristics of the constituent block copolymers and the preparation process, it is possible to improve the typical features of micelles, including particle size, shape, drug loading, cellular internalization, stability and drug release kinetics.[47] To test its antibacterial efficacy, a thermo-sensitive co-polymeric micelle made by radical co-polymerization and Nigella sativa extract is entrapped in this polymeric system. More efficient than other forms was a polymeric micelle filled with Nigella sativa. When the infectious condition is functioning, the thermo-sensitive polymeric system would deliver the medication into the body more efficiently.[48]

CONCLUSION

The creation of a novel drug delivery system holds great promise for the herbal formulation industry because it is a safe, efficient, convenient and cost-effective drug delivery method. It can also help to solve issues related to the herbal formulation industry, improve its efficiency and increase its bioavailability through increased solubility, controlled release and target orientation. The resultant novel herbal formulation will not only boost the herbal drug market globally but also improve human therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NDDS: Novel Drug Delivery System; **BCS:** Biopharmaceutical Classification System; **HNDDS:** Herbal Novel Drug Delivery System; **Hb:** Haemoglobin; **CVS:** Cardio Vascular System; **THC:** Tetrahydrocannabinol; **GIT:** Gastrointestinal Tract; **ALT:** Alanine Transaminase; **AST:** Aspartate Transaminase.

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