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NOVEL DRUG DELIVERY SYSTEMS OF HERBAL MEDICINE

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ABSTRACT: Over the past several years, great advances have been made in developing novel drug delivery systems (NDDS) for plant actives and extracts. Various novel herbal formulations such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, animations, microsphere, transfersomes, and ethosomes have been reported using proactive and plant selections. The novel formulations are reported to have remarkable 0 advantages over conventional formulations of plant actives and extracts, which include a cement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. Phytosome is a patented technology developed by a leading maker of drugs and nutraceuticals to incorporate standardized plant extracts or water-soluble phytoconstituents into phospholipids to produce lipid-compatible molecular complexes. The herbal drugs can be used in a more upright course with enhanced efficacy by incorporating them into modern dosage forms. The present review highlights the current status of developing novel herbal formulations. It summarizes their preparation method, type of active ingredients, size, entrapment efficiency, route of administration, biological activity, and applications of novel formulations.

INTRODUCTION: In the past few decades, considerable attention has been Concentrated on the evolution of novel drug delivery. The novel carriers should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a Rate directed by the body's needs throughout Treatment. Secondly, it should channel the active entity of the herbal drug to the site of action. Conventional dosage forms, including prolonged-release dosage forms, cannot meet any of these. In phyto formulation research, developing nanosystem (NDDS) for herbal drugs.

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Dosage forms (polymeric nanoparticles and nanocapsules, Liposomes, solid lipid nanoparticles, phytosomes Nanoemulsion, *etc*.) have several advantages for herbal drugs, including enhancement of solubility and bioavailability, pro-M Tection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation, etc.

Thus the nano-sized novel drug delivery systems of herbal drugs have a potential future for Enhancing the activity and overcoming problems associated with plant medicines. Liposomes, which are biodegradable and essentially non-toxic vehicles, can encapsulate hydrophilic and hydrophobic materials [1]. Liposome-based drug Delivery systems offer the potential to enhance the therapeutic Index

of anti-cancer agents, either by increasing the drug concentration in tumor cells and/or by decreasing the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon and utilizing targeting strategies [2]. The main advantages of using liposomes include: i) the high biocompatibility, ii) the easiness of preparation, iii) the chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds, and iv) the simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components [3]. Delivery of agents to the reticuloendothelial system (RES) is easily achieved since most conventional liposomes are trapped By the RES [1]. Applying novel approaches can also improve the efficacy of herbal cosmetic formulations on the Human body [4].

Similarly, the other vesicular systems like Nanoemulsion, ethosomes, and transferases are highly useful assemblies and find various advantages in the delivery of herbal medicines; some are summarized in the present article. The phytosome process has also been applied to many popular herbal extracts, including Ginkgo biloba, grape seed, Hawthorn, milk thistle [5], green tea, and ginseng. These herbal extracts' Flavonoid and terpenoid components lend themselves quite well for directly binding to Phosphatidylcholine. Phytosome is produced by binding Individual components of herbal extracts to phosphatidyl Choline, resulting in a dosage form that is better absorbed. Thus, produces better results than the conventional herbal Extracts [6].

The results indicate that the absorption of silybin from silybin phytosome is approximately seven times greater Compared to the absorption of silybin from regular milk Thistle extract [5]. Drugs can be embedded or dissolved in Nanoparticles and can also be adsorbed or coupled on the Surface [7]. Encapsulating drugs within NPs can improve the solubility and pharmacokinetics of drugs and, in some cases, enable further clinical development of new chemical entities that have stalled because of poor pharmacokinetic properties [8]. The major carrier materials of nanoparticles are synthetic Biodegradable high molecular polymers and natural polymers. The former usually includes poly-α-cyanoacrylate alkyl Esters, polyvinyl alcohol, polylactic acid, and polylactic-Glycolic acid. The latter is usually divided into two classes: Proteins (albumin, gelatin and vegetable protein) and Polysaccharides (cellulose, starch and its derivatives, alginate, Chitin, and chitosan, *etc*.) [9]. In this article, an attempt has been made to touch upon Different aspects related to the development of novel herbal formulations, including method of preparation, type of active ingredient, entrapment efficiency, and applications, *etc*.

Types of Novel Herbal Drug Delivery Systems: Several approaches in case of new herbal drug delivery system include different types of expressions such as mouth-dissolving tablets, liposomes, phytosomes, pharmacosomes, museums, nanoparticles, microspheres, transfersomes, ethosomes, transdermal drug delivery system (TDDS), and proniosomes are discussed Mouth-dissolving tablets: Asoka Lifescience Limited launched Res-Q, the world's first Polyherbal mouth-dissolving tablet, fast mouth-dissolving drug. It induces a new drug delivery system that imparts increased efficacy. In the Ayurvedic medicine segment; is the inaugural Attempt to make medicines more effective in managing chronic Ailments. Res-Q is a polyherbal medicine highly effective for Lung problems and other respiratory ailments such as asthma. This unique mouth-dissolving drug delivery system ensures that the drug reaches the blood immediately and bypasses the first-pass Metabolism. It dissolves in the mouth by mixing with the saliva and gets absorbed. This Res-Q provides relief from Respiratory distress within 15 min. Hence, the product resembles Sorbitrate's efficacy, a revolutionary Mouth-dissolving drug used in cardiac distress [10].

Liposomes: The liposomes are spherical particles that encapsulate a Fraction of the solvent, in which they freely diffuse (float) into their interior. They can have one, several, or multiple Concentric membranes. Liposomes are constructed of polar Lipids characterized by having a lipophilic and Hydrophilic group on the same molecules [11]. Upon Interaction with water, polar lipids self-assemble and form Self-organized colloidal particles. Simple examples are deter-Gents; components form micelles, while polar lipids with Bulkier hydrophobic parts cannot associate micelles with High curvature radii but form bilayers that can self-

close into liposomes or lipid vesicles. A cross-section of a liposome **Fig. 1** depicts the hydrophilic heads of the amphiphile orienting towards the water compartment. In contrast, the lipophilic tails orient away from the water towards the center of the vesicle, thus forming a bilayer.

Consequently, water-soluble compounds are entrapped in the water compartment and aggregate in the lipid section. Uniquely, liposomes can encapsulate both hydrophilic and Lipophilic materials. Liposomes usually formed from phospholipid's have been used to change the pharmacokinetics Profile of drugs, herbs, vitamins, and enzymes. A Variety of herbal liposomal formulations has been studied, summarized in **Table 1**. Because of their unique properties, liposomes can enhance the performance of Products by increasing ingredient solubility, improving Ingredient bioavailability, enhancing intracellular uptake, and altering pharmacokinetics and biodistribution [12] and *in-vitro* and *in-vivo* stability. Liposomes as a drug delivery system can improve drugs' therapeutic activity and safety, mainly by delivering them to their site of action and maintaining Therapeutic drug levels for prolonged periods [13–14]. Milk thistle (Silybummarianum) is one of the few herbal Drugs whose excellent pharmacological profile readily provides proof of clinical efficacy [15].

Meanwhile, silymarin is poorly absorbed (20–50%) from the gastrointestinal tract [16]. That causes the effects of silybin, one of the main active Flavonoids commonly found in dried fruits of silymarin, to be greater after parenteral than oral administration [17].

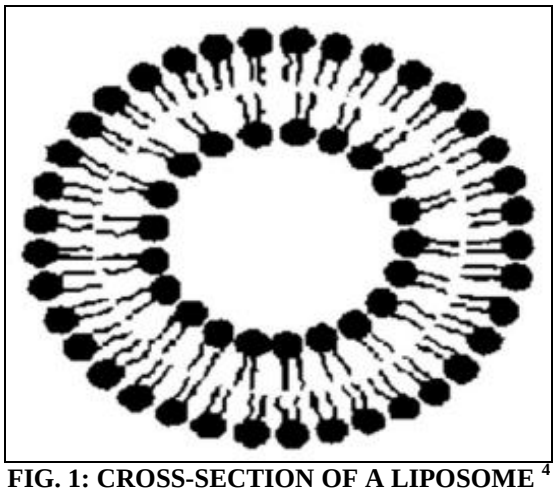

FIG. 1: CROSS-SECTION OF A LIPOSOME [4]

TABLE 1: HERBAL FORMULATIONS IN LIPOSOMAL DRUG DELIVERY SYSTEMS

Plants/constituents	Therapeutic category	Applications with respect to liposomal technology	Reference
Ampelopsin	Anticancer	Improved therapeutic efficacy	18
Capsaicin	Analgesic	Prolong action, permeation enhancement	19
Curcumin	Anticancer	Long systemic residence time and high entrapment efficiency	20
Paclitaxel	Anticancer	pH sensitivity and improved entrapment efficiency	21
Usnic acid	Antimycobacterial	Prolong action and solubility enhancement	22
Wogonin	Anticancer	Prolong duration of action	23
Quercetin and rutin	Hemoglobin	Enhancement of Hemoglobin binding	24
Garlicin	Lungs	Increase efficiency	25
Catechins	Antioxidant and chemopreventive	Increased permeation through skin	26
Breviscapin	Cardiovascular diseases	Sustained delivery of breviscapine	27

Nanoparticles: In recent years, the nanonization of herbal medicines has attracted much attention; [28] of them are illustrated in **Table 2.** Nanoparticles and Nanoemulsions **Fig. 2** are Colloidal systems with particles varying in size from 10 nmTo 1000 nm [29, 30]. Nanoparticle systems with mean particle Size well above the 100 nm standard have also been reported In literature, including nanonizedcurcuminoids [31], pacli-Taxel [32] and praziquantel [33] which have a mean particle Size of 450, 147.7, and even higher than 200 nm, respectively. IN addition, nanoparticles could also be defined as being Submicronic (b1 lm) colloidal systems [34]. The nanospheres Have a matrix type structure in which the active ingredient is Dispersed throughout (the particles), whereas the Nano capsules have a polymeric membrane and an active ingredient Core. Nanonization possesses many advantages, such as increasing compound solubility, reducing medicinal doses, and improving the absorbency of herbal medicines compared with the respective crude drugs preparations [35].

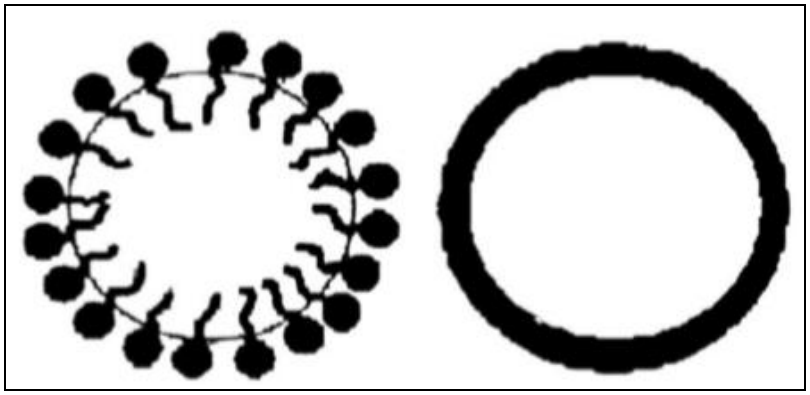

FIG. 2: CROSS-SECTION OF (A) NANOEMULSION AND (B) BIOPOLYMERIC NANOPARTICLES [4]

TABLE 2: HERBAL NANOPARTICULATE DRUG DELIVERY SYSTEM

Plants/constituents	Therapeutic category	Applications Wrt Nanotechnology	Reference
Triptolide nanoparticle	Anti-inflammatory	Enhance the penetration of drugs through the stratum corneum by increased hydration	36
Artemisinin nanocapsules	Anticancer	Sustained drug release	37
Texel nanoparticle	Anticancer	Enhance the bioavailability and sustained drug release	38
Berberine nanoparticle	Anticancer	Sustained drug release	39
Curcuminoids solid lipid Nanoparticle	Anticancer	Prolonged release of the curcuminoids	40
Camptothecin encapsulated Nanoparticle	Anticancer	Prolonged blood circulation and high accumulation in tumors	41
Naringenin nanoparticle	Hepatoprotective	Improved the release of NAR and improved its solubility	42
Breviscapine nanoparticle	Cardiovascular and cerebrovascular	Prolong the half-life and decrease RES uptake	43
Tetrandrine nanoparticle	Lung	Sustained drug release	44
Glycyrrhizic acid nanoparticle	Anti-inflammatory, antihypertensive	Improve the bioavailability	45

Phytosome: Over the past century, phytochemical and phytopharmacological sciences established the compositions, biological Activities, and health-promoting benefits of numerous plant Products. Most of the biologically active constituents of plants are polar or water-soluble molecules. However, water-soluble Phytoconstituents (like flavonoids, tannins, terpenoids, *etc*.) are poorly absorbed either due to their large molecular size, Which cannot absorb by passive diffusion, or due to their poor Lipid solubility, severely limiting their ability to pass across The lipid-rich biological membranes, resulting poor bioavailability [46]. It has often been observed that the isolation and Purification of the constituents of an extract may lead to a Partial or total loss of specific bio-activity for the purified Constituent the natural constituent synergy becomes lost. Very often, the chemical complexity of the crude or partially purified extract seems essential for the active constituents' bioavailability. When taken orally, some Constituents may be destroyed in the gastric environment. As Standardized extracts are established, poor bioavailability often limits their clinical utility due to above said reasons. It has been observed that complexation with certain other clinically useful nutrients substantially improves the bioavailability of such extracts and their individual constituents. The nutrients so helpful for enhancing absorption are the Phospholipids. Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals to incorporate standardized plant extracts or water-soluble Phytoconstituents into phospholipids to produce lipid-compatible molecular complexes, called phytosomes and so vastly improve their absorption and bioavailability [47] **Table 3**. In liposomes no chemical bond is formed; the Phosphatidylcholine molecules surround the water-soluble substance. Hundreds or even thousands of Phosphatidylcholine molecules may surround the water-soluble compound. In contrast, with the phytosome process, the Phosphatidylcholine and the plant components actually form A 1:1 or a 2:1

molecular complex depending on the substance (s) complexed, involving chemical bonds **Fig. 3**. Phospholipids are complex molecules that are used in all known life Forms to make cell membranes. In humans and other higher animals, the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water-miscible nutrients. They are miscible in water and Lipid environments and are well absorbed orally. Phytosomes are more bioavailable than conventional herbal extracts due to their enhanced capacity to cross the lipoidal Bio membrane and finally reach the systemic circulation.

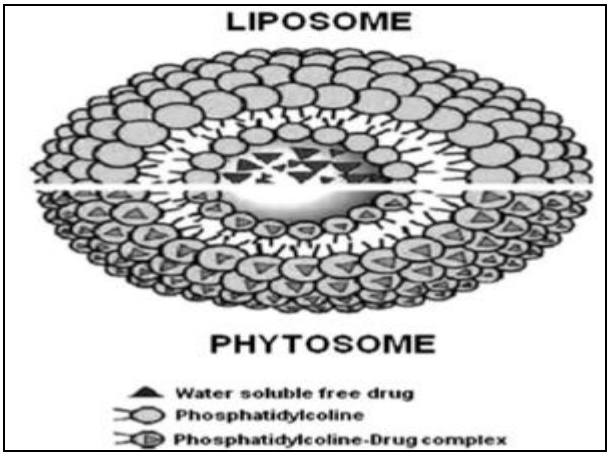

FIG. 3: DIFFERENCE BETWEEN LIPOSOME AND PYTOSOME [58]

TABLE 3: APPLICATIONS WRT PHYTOSOMAL TECHNOLOGY

Plants/constituents	Therapeutic category	Applications Wrt Phytosomal technology	Reference
Ginkgo biloba	Cardioprotective, antioxidant activity	Flavonoids of GBP stabilize the ROS	48
Ginsenosides	Nutraceutical, immunomodulator	Increase absorption	49
Curcumin	Antioxidant, anticancer	Increase antioxidant activity and increase bioavailability	50
Quercetin	Antioxidant, anticancer	Exerted better therapeutic efficacy	51
Epigallocatechin	Nutraceutical, systemic antioxidant, anticancer	Increase absorption	52
Naringenin	Antioxidant activity	Prolong duration of action	53
Silybin	Hepatoprotective, antioxidant for liver and skin	Absorption of silybin phytosome from silybin is approximately 7 times greater	54

Ethosomes: Newer advancements in patch technology have led to the development of ethosomal patch, which consists of the drug in ethosomes. Ethosomal systems are made up of soya Phosphatidylcholine, ethanol, and water. They may form Multilamellar vesicles and have a high entrapment capacity For particles of various lipophilicities. The elastic vesicles and transfersomes have also been used as drug carriers for a range of small molecules, peptides, proteins and vaccines [55]. Ethosome has a high deformability and entrapment efficiency and can penetrate through the skin completely and improve Drug delivery through the skin. Likened to other liposomes, the Physical and chemical properties of ethosomes make the legal Transfer of the drug through the stratum corneum into a deeper Skin layer efficiently or even into the blood circulation [56]. This property is important as the topical drug carrier and Transdermal delivery system. Moreover, the ethosomes carrier Also can provide an efficient intracellular delivery for both Hydrophilic and lipophilic drugs [57] percutaneous absorption of matrine an anti-inflammatory herbal drug, is increased [58]. It also permits the antibacterial Peptide to penetrate the Fibrocyte easily [59]. From the review of the literature it has been observed that, only three clinical trials have been conducted on ethosomal Systems in human volunteers. Horwitz *et al.* carried out a Pilot, double-blind, randomized clinical study to compare the efficacy of an ethosomal acyclovir preparation and commercially available acyclovir cream (Zovirax®) in treating recurrent herpes labialis in 40 human volunteers. The results revealed that the ethosomal acyclovir preparation performed Betterthan Zovirax cream and showed significant improvement in all the evaluated clinical parameters, such as the time of crust Formation and disappearance and pain parameters. The efficacy of ethosomal gel of clindamycin phosphate and salicylic acid was evaluated in a pilot clinical trial of 40 acne patients treated with the gel twice daily for 8 weeks. Volunteers treated with Ethosomal gel showed considerable improvement in acne Condition, with fewer comedies, pustules, and total lesions compared to placebo. Ethosomal Preparation of prostaglandin E1 was evaluated in a pilot clinical Study in patients with erectile dysfunction. It was observed that 12 of 15 tested

patients had improved peak systolic velocity and penile rigidity. Erection duration was 10–60 min. There was no reported adverse skin reactions associated with the Treatment in any of the aforementioned clinical trials [60] **Table 7** shows the Clinical data of ethosomes [61].

TABLE 4: THERAPEUTIC WRT NANOTECHNOLOGY

Plants/constituents	Applications category	Therapeutic Wrt Nanotechnology	Reference
Capsaicin transfersomes	Analgesic	Increase skin penetration	62
Colchicine transfersomes	Antigout	Increase skin penetration	63
Vincristine transfersomes	Anticancer	Increase entrapment efficiency and skin	64
Matrine ethosomes	Anti-inflammatory	Improve the percutaneous permeation	65
Ammonium glycyrrhizinate ethosomes	Anti-inflammatory	Increase of the in vitro percutaneous permeation	66

Emulsion: Emulsion refers to a non-homogeneous dispersion system that is composed of two kinds of liquids unable to dissolve each Other, one of which disperse in the other one in the form of Droplets [67]. Generally, the emulsion is composed of oil phase, Water phase, surfactant and sub-surfactant. Its appearance is Translucent to transparent liquid. The emulsion can be classified as Intoordinary emulsion (0.1–100 μm), micro-emulsion (10– 100 nm), sub-micro-emulsion (100–600 nm), *etc*. **Table 4** Among them, the micro-emulsion is also called Nanoemulsions, and the sub-micro-emulsion is also called lipid emulsion.

As a Drug delivery system, emulsion distributes *in-vivo* in the Targeted manner due to its affinity to the lymph. In addition, the drug can be sustained release in a long time because the drug is packaged in the inner phase and kept off direct touch with the Body and tissue fluid [68]. After the oily drugs or lipophilic Drugs being made into O/W or O/W/O emulsion, the oil droplets Are phagocytosised by the macrophage and get a high Concentration in the liver, spleen, and kidney in which the Amount of the dissolved drug is very large. While water-soluble drug is produced into W/O or W/O/W emulsion, it can be easily Concentrated in the lymphatic system by intramuscular or Subcutaneous injection. The size of the emulsion particle has an Impact on its target distribution. Apart from its targeted sustained release, producing the Herbal drug into emulsion will also strengthen the stability of The hydrolyzed materials, improve the penetrability of drugs to The skin and mucous, and reduce the drugs' stimulus to tissues. So far, some herbal drugs, such as camptothecin, *Brucea Javanica* oil, coixenolide oil and zedoary oil, have been made into emulsions.

For example, Zhou *et al*. [69] studied the Influence of the elemenum emulsion on the human lung Adenocarcinoma cell line A549 and protein expression. Results showed that the elemenum emulsion has a significant Inhibition on the growth and proliferation of the A549 *in-vitro* and it showed a time and dose-dependent relationship. Elemenum emulsion is a type of new anti-cancer drug with Great application prospects. Furthermore, it has no marrow Inhibition and no harm to the heart and liver.

TABLE 5: THERAPEUTIC WRT NANOTECHNOLOGY

Plants/constituents	Applications category	Therapeutic Wrt Nanotechnology	Reference
Self-nanoemulsifying Zedoary	Hepatoprotection anticancer	Improved aqueous	70
essential oil	Anti-inflammatory	dispersibility, stability and oral dispersibility, bioavailability	71
Triptolide microemulsion	Anti-inflammatory	Enhance the penetration of drugs through the stratum corneum by increased hydration	72
Docetaxel submicron Emulsion	Anticancer	Improve residence time	73
Berberine nanoemulsion	Anticancer	Improve residence time and absorption	74
Silybin nanoemulsion	Hepatoprotective	Sustained release formulation	75
Quercetin microemulsion	Antioxidant	Enhance penetration into stratum corneum and epidermis	76

Marketed Herbal Novel Drug Delivery Formulations: Two companies dominate the market for these systems, Namely, Cosmetochem and Indena. For herbal drug delivery,

Cosmetochem launches Herbasec® technology in markets which are liposomal preparations of various herbal Ingredients such as extracts of White tea, Green tea, white Hibiscus, Gurana, and Aloe Vera. These extracts are used in Cosmetics because of their anti-oxidant effects to prevent aging. Indena patented the technology of phytosomes® and launched many products in the market with Diverse therapeutic benefits. Indena commercializes the plant Constituents/extracts of liquorice (18 ß – glycy-rrhetinic acid), *Ammi visnaga* (visnadin), *Centella asiatica* (triterpenes), *G. biloba* (ginkgo flavonglucosides, ginkgolides, bilobalide), Hawthorn flower (vitexin-2″-O-rhamnoside), milk thistle (silymarin and Silybin), horse chestnut (escin ß-sitosterol), *Terminalia sericea* (sericoside), *Panax ginseng* (ginsenosides), Grape seed (polyphenols), Green tea (polyphenols), *etc* [77].

CONCLUSION: Herbal medications have been widely employed all over the globe since ancient times and have been acknowledged by doctors and patients for their better therapeutic value as they cause fewer adverse effects compared with modern Medications. The drugs of Ayurvedic origin can be utilized in a more upright course with enhanced efficacy by incorporating modern dosage forms.

However, phytotherapeutics needs a scientific approach to render the components in a new way to Increase patient compliance and avoid repeated administration. This can be accomplished by designing NDDS for herbal Ingredients. NDDS not only reduces the repeated administration to overcome noncompliance but also helps increase the Therapeutic value by reducing toxicity and increasing bioavailability. Recently, pharmaceutical scientists.

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