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# Novel drug delivery systems for herbal drugs

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## ABSTRACT

Novel drug delivery systems(NDDS) for herbal drugs with poor water solubility have been expanding, almost exponentially, over the past six years. The great advancement has been made for the technologies increasing the commercial potential of the herbal formulations by increasing the patient compliance and avoiding repeated administration of the formulation. There are varieties of novel herbal formulations like nanoparticles, matrix systems, solid dispersions, nanocapsules, liposomes, phytosomes, nanoemulsions, microemulsions, microsphere, micropellets, transferosomes, and ethosomes has been reported using bioactive and plant extracts. These formulations have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, therapeutic efficacy, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. This review highlights the current status of the development of novel herbal formulations and applications of NDDS in the traditional medicine system to conflict more chronic diseases like asthma, diabetes, cancer and others.

**Keywords:** Herbal drugs, NDDS, liposomes, phytosomes, nanoparticles, nanotechnology.

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## 1. Introduction

Herbal medicines have been widely used all over the world since ancient times and have been recognized for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. The activity of herbal medicines depends on overall function of a variety of active components, as all the constituents provide synergistic action and thus enhance the therapeutic value. Each active constituent plays an important role and they are all related to each other. However, the most important limitations of the herbal drugs include the presence of thousands of constituents which works simultaneously against the diseases, the insoluble character of the constituents leading to lower bioavailability and increased systemic clearance requiring repeated administration or higher dose, which makes the drug as a poor candidate for therapeutic use[1]. Therefore, phytotherapeutics needs a scientific approach to deliver the components in a manner to increase patient compliance and avoid repeated administration. This can be achieved by incorporation of the herbal extracts into novel formulation systems which can add certain advantages to the conventional dosage form by reducing the dosing volume, increasing the bioavailability and reducing the frequency of the dose administration to overcome non-compliance[2]. For a long time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex polyherbal systems. However, modern phytopharmaceutical research solves the scientific needs for herbal medicines as in modern medicine, which gives way for developing novel formulations such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and others [3].

Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach. The novel carriers should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity of herbal drug to the site of action. These novel drug delivery systems not only reduce the repeated administration to overcome non-compliance, but also help to increase the therapeutic value by reducing toxicity, increasing the bioavailability, enhancement of solubility, 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[4].

### 1.1 Need of novel drug delivery system for herbal medicines

Herbal drugs are becoming more popular in the modern world for their application to cure variety of diseases with less toxic effects and better therapeutic effects. Most of the biologically active constituents of plants are 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[5]. 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 to be essential for the bioavailability of the active constituents. Extracts 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. Therefore, for good bioavailability, natural products must have a good balance between hydrophilicity (fordissolving into the gastrointestinal fluids) and lipophilicity (to cross lipidicbiomembranes)[6]. Manyphytoconstituents like polyphenolics have good water solubility, but are, nevertheless, poorly absorbed either due to their multiple-ring large size molecules which cannot be absorbed by simple diffusion, or dueto their poor miscibility with oil and other lipids, severely limiting their ability to pass

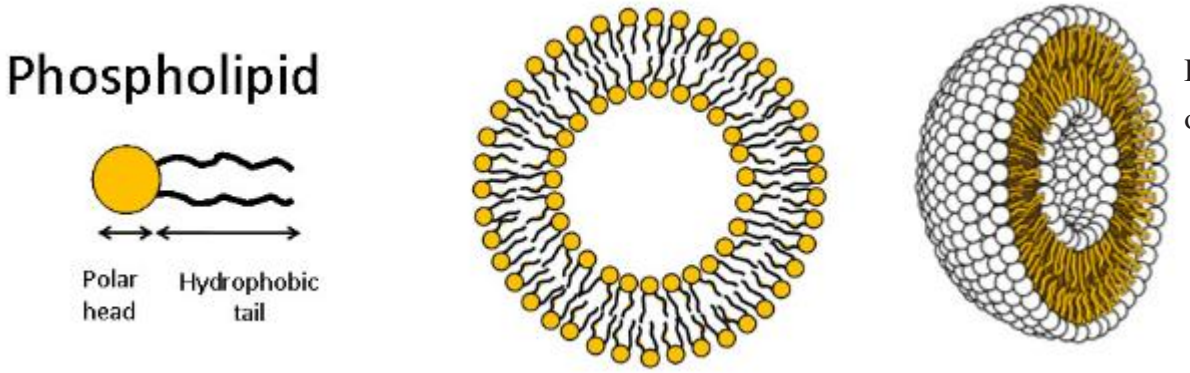


Fig 1.Structure of a liposome

Table 1: Liposomal herbal formulation

| S.No. | Formulations | Active ingredients | Applications of liposome formulations | Biological activity |
|---|---|---|---|---|
| 1 | Liposomes encapsulated silymarin | Silymarin | Improve bioavailability | Hepatoprotective |
| 2 | Liposoma artemisia arborescens | Artemisia arborescens essential oil | Targeting of essential oils to cells, enhance penetration into, cytoplasmatic barrier | Antiviral |
| 3 | Paclitaxel liposome | Paclitaxel | High entrapment efficiency and PH sensitive | Anticancer |
| 4 | Curcumin liposome | Curcumin | Long-circulating with high entrapment efficiency | Anticancer |
| 5 | Flavonoids liposomes | Quercetin and rutin | Binding of flavonoids with Hb is enhanced | Hemoglobin |
| 6 | Colchicine Liposome | Colchicine | Enhance skin accumulation, prolong drug release and improve site specificity | Antigout |
| 7 | Catechins liposomes | Catechins | Increased permeation through skin | Antioxidant and chemopreventive |
| 8 | Quercetin liposomes | Quercetin | Reduced dose, enhance penetration in blood brain barrier | Antioxidant & Anticancer |

across the lipid –richouter membranes of the enterocytes of the small intestine[7].

Incorporation of novel drug delivery technology to herbal or plant actives minimizes the drug degradation or pre systemic metabolism and serious side effects which helps in carrying optimum amount of the drug to their site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism and increase the prolonged circulation of the drug into the blood due to their small size[8]. It has also 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 the absorption are the phospholipids.

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.

## 2. Types of Novel Herbal Drug Delivery Systems

Various approaches in case of novel herbal drug delivery system were used with herbal drugs and phytochemicals which may be broadly classified into the following groups:

1. Vesicular delivery systems, which include liposomes, phytosomes, ethosomes, transferosomes

2. Particulate delivery systems, which include microspheres, nanoparticles, micropellets

3. Biphasic systems, such as micro/ nano emulsions

### 2.1. Liposomes

These are micro-particulate or colloidal carriers, usually 0.05-5.0μm in diameter which forms spontaneously when certain lipids are hydrated in aqueous media. The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse or float into their interior. They can have one, several or multiple concentric membranes[9]. Liposomes are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules. Upon interaction with water, polar lipids self-assemble and form self-organized colloidal particles[10].

Simple examples are detergents; components form micelles, while polar lipids with bulkier hydrophobic parts cannot associate into micelles with high curvature radii but form bilayers which 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 while the lipophilic tails orient away from the water towards the center of the vesicle, thus forming a bilayer[11]. Consequently, water soluble compounds are entrapped in the water compartment and lipid soluble compounds aggregate in the lipid section. Uniquely, liposomes can encapsulate both hydrophilic and lipophilic materials. Liposomes usually formed from phospholipids, have been used to change the pharmacokinetics profile of several herbal drugs (Table 1). Because of their unique properties liposomes are able to enhance the performance of products by increasing ingredient solubility, improving ingredient bioavailability, enhanced intracellular uptake and altered pharmacokinetics and biodistribution and in vitro and in vivo stability. Liposomes as a drug delivery system can improve the therapeutic activity and safety of drugs, mainly by delivering them to their site of action and by maintaining therapeutic drug levels for prolonged periods of time[12].

### 2.2 Phytosome

The term “phyto” means plant while “some” means cell-like. Phytosomes are little cell like structure (Fig 2.) which are prepared by reacting from 3-2 moles but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine with one mole of component for exampleflavolignanans, either alone or in the natural mixture in aprotic solvent such asdioxane or acetone from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbons or lyophilization or by spary drying[13]. In the complex formation of phytosomes the ratio between these two moieties is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1. In the phytosome preparations, phospholipids

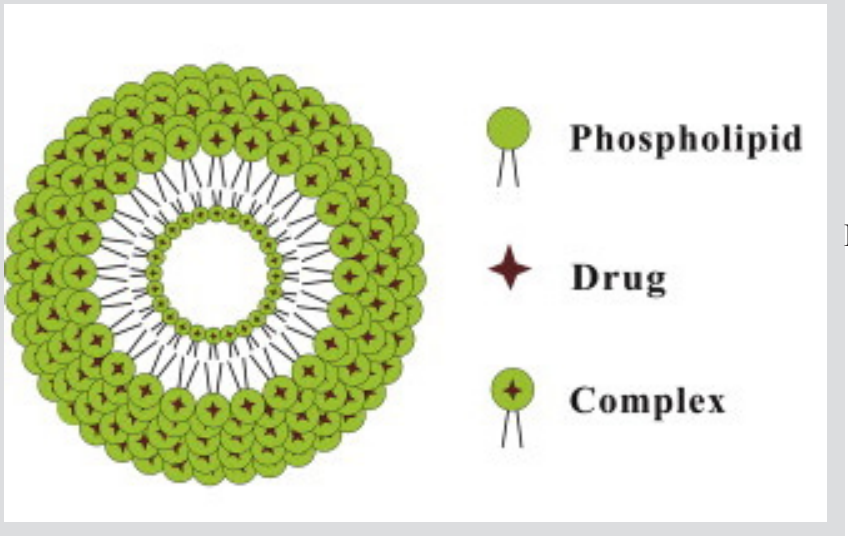


Fig 2. Structure of Phytosome

Table 2: Commercial phytosomes products

| S.No. | Formulations | Phytoconstituentscomplexed | Dose | Indications |
|---|---|---|---|---|
| 1 | Ginkgo phytosome | 24% ginkgoflavonoids | 120mg | Protects brain and vascular linings |
| 2 | Silybinphytosome | Silybin | 120mg | Hepatoprotective, antioxidant for liver and skin |
| 3 | Hawthorn phytosome | Flavonoids from Crataegus sp. | 100mg | Cardio protective & antihypertensive |
| 4 | Green tea phytosome | Epigallocatechin | 5 0 -100mg | Antioxidant & anticancer |
| 5 | Ginseng phytosome | 37.5% ginsenosides | 10mg | Immunomodulator |

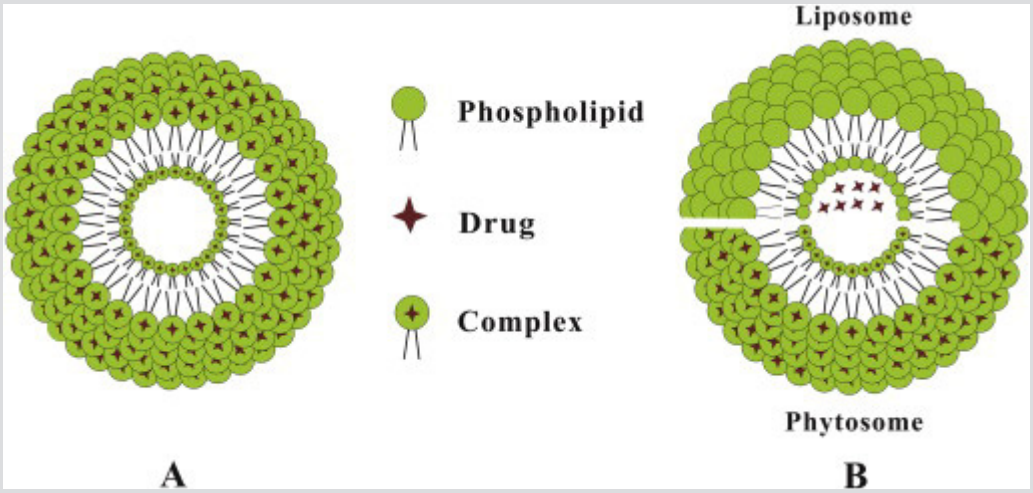


Fig 2. Structure of Phytosome

Table 3. Nano structured herbal formulations

| S.No. | Formulations | Active ingredients | Applications of nanostructured formulations | Biological activity | Route of administration |
|---|---|---|---|---|---|
| 1 | Artemisinin nanocapsules | Artemisinin | Sustained drug release | Anticancer | In vitro |
| 2 | Nanoparticles of *Cuscuta chinensis* | Flavonoids and lignans | Improve water solubility, | Hepatoprotective and antioxidant effects | Oral |
| 3 | Triptolide nanoparticle | Triptolide | Enhance the penetration of drugs through the stratum corneum by increased hydration | Anti-inflammatory | Topical (skin) |
| 4 | Taxel-loaded nanoparticles | Taxel | Enhance the bioavailability and sustained drug release | Anticancer | – |
| 5 | Berberine-loaded nanoparticles | Berberine | Sustained drug release | Anticancer | In vitro |
| 6 | Silibini-loaded nanoparticles | Silibini | High entrapment efficiency and stability | Hepatoprotective | – |
| 7 | Glycyrrhizic acid-loaded nanoparticles | Glycyrrhizic acid | Improve the bioavailability | Anti-inflammatory, antihypertensive | – |
| 8 | Quercetin-loaded nanoparticles | Quercetin | Increase antioxidant activity and release of the drug 74 times higher | Antioxidant | |

are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3- rhamnoside, hyperoside, vitexine, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolinglucoside, ginkgonetine, isoginkgonetine and bilobetine[14]. Some liposomal drugs complex operate in the presence of the water or buffer solution where as phytosomes operate with the solvent having a reduced dielectric constant. Starting materials like flavonoids are insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming phytosomes. This chemical and physical property change is due to the formation of a true stable complex[15].

Most of the bioactive constituents of phytomedicines are water-soluble compounds like flavonoids, glycosides; terpenoids in which flavonoids are a major class of bioactive compounds possesses broad therapeutic activities. Because of water soluble herbal extract and lipophilic outer layer phytosomes exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts. Phytosome technology has been effectively used to enhance the bioavailability of many popular herbal extracts (Table 2) including milk thistle, ginkgo biloba, grape seed, green tea, hawthorn, ginseng etc and can be developed for various therapeutic uses[16].

**Differencebetween Phytosome and Liposome** -Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. Here, no chemical bond is formed; the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding 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) complexes, involving chemical bonds[17]. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care products (Fig. 3).

### 1.3 NANOPARTICLES

The nanoparticles have come forward as the capable approach in drug delivery systems for the well-organized delivery of drugs utilized in the treatment of various diseases such as cancer by crossing the reticuloendothelial system, enhanced permeability and retention effect, and tumor-specific targeting. The major goal behind designing nanoparticle as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen[18].

The size range for nanoparticles and nanoemulsions (Fig. 4)varies from 10 nm to 1000 nm. Nanoparticle systems with mean particle size well above the 100 nm standard have also been reported in literature, including nanonized curcuminoids, paclitaxel and praziquantel 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 (< 1 lm) colloidal systems. The nanospheres have a matrix type structure in which the active ingredient is dispersed throughout (the particles), whereas the nanocapsules have a polymeric membrane and an active ingredient core[19]. Nanonization possesses many advantages, such as increasing compound solubility, reducing medicinal doses, and improving the absorbency of herbal medicines (Table 3) compared with the respective crude drugs preparations.

### 2.4. EMULSIONS

Emulsion is a biphasic system in which one phase in intimately dispersed in the other phase in the form of minute droplets. Generally, emulsion is composed of oil phase, water phase, surfactant and sub-surfactant. Its appearance is translucent to transparent liquid. Emulsion can be classified into ordinary emulsion (0.1-100 μm), micro-emulsion (10-100 μm) and sub-microemulsion (100-600 μm)[20]. Among them, the micro-emulsion is also called nano-emulsion and

Fig 4. Cross-section of (a) nanoemulsion and (b) biopolymeric nanoparticle.

Table 4. Emulsion herbal formulations.

| S.No. | Formulations | Active ingredients | Applications of emulsion formulations | Biological activity | Route of administration |
|---|---|---|---|---|---|
| 1 | Self-nanoemulsifying Zedoary essential oil | Zedoary turmeric oil | Improved aqueous dispersibility, stability and oral bioavailability. | Hepatoprotection anticancer and anti-bacterial | Oral |
| 2 | Triptolide micro-emulsion | Triptolide | Enhance the penetration of drugs through the stratum corneum by increased hydration | Anti-inflammatory | Topical |
| 3 | Docetaxel submicron emulsion | Docetaxel | Improve residence time | Anticancer | Intravenous |
| 4 | Berberine nanoemulsion | Berberine | Improve residence time and absorption | Anticancer | Oral |
| 5 | Silybin nanoemulsion | Silybin | Sustained release formulation | Hepatoprotective | Intramuscular |
| 6 | Quercetin micro-emulsion | Quercetin | Enhance penetration into stratum corneum and epidermis | Antioxidant | Topical |

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. 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[21].

Emulsion can release the drug for a long time because it is packed in the inner phase and makes direct contact with the body and other tissues. Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of hydrolyzed materials, improve the penetrability of drugs to the skin and mucous and reduce the drugs stimulus to tissues. The new type, viz., Elemenum emulsion, is uses as anti-cancer drug and safer for heart and liver. Emulsion formulation for various herbal bioactive have been reported and depicted in Table 4. Emulsion of Taxus brevifolia (Docetaxel), Sophora japonica (Quercetin) and Tripterygium wilfordii (Triptolide) were prepared by homogenization method that improves the bioavailability, absorption, penetration into stratum corneum and epidermis and sustained release of these drugs. Rheum rhabarbarumi (Rhubarb) uses as laxative, anti-bacterial and anti-spasmodic, the conventional dose suffering from poor solubility and require high drug concentration for desired biological activity, the emulsion prepared by miceller electro-kinetic method provides better bioavailability and good penetration ability of rhubarb[22].

## 2.5. TRANSFEROSOMES

Transfersome, which was first introduced in the early 1990s, is an ultradeformable vesicle, elastic innature which can squeeze itself through a pore which is many times smaller than its size owing to its elasticity.Transfersomes are applied in a non-occluded method to the skin and have been shown to permeate through thestratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin[23]. Transfersomesare made up of a phospholipids component along with a surfactant mixture (Fig 5). The ratio of individual surfactantsand total amount of surfactants control the flexibility of the vesicle. The uniqueness of this type of drug carriersystem lies in the fact that it can accommodate hydrophilic, lipophilic as well as amphiphilic drugs. These drugsfind place in different places in the elastic vesicle before they get delivered beneath the skin[24].

It can be applicable as drug carriers for a range of small molecules, peptides, proteins and herbal ingredients (Table 5). Transferosomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting maintenance of skin in this connection the transferosomes of Capsaicin has been prepared which shows the better topical absorption in comparison to pure capsaicin[25].

## 2.6. Ethosomes

Ethosomes are phospholipids-based elastic nano-vesicles (Fig 6) having high content of ethanol (20%-45%). Ethanol is known as an efficient permeation enhancer and has been reported to be added in the vesicular system to prepare the elastic nano-vesicles. Ethosomes were developed as novel lipid carriers composed of ethanol, phospholipids and water and to improve the delivery of various drugs to the skin[26]. It enables drugs to reach the deep skin layers and/ or systemic circulation. Due to high content of ethanol, the lipid membrane is packed less tightly in comparison with conventional vesicles, but it has equivalent stability. This property is very 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, percutaneous absorption of matrine an anti-inflammatory herbal drug is increased (Table 6). It also permits the antibacterial peptide to penetrate into the fibrocyte easily[27]. Ethosomes can be used for the delivery of diverse group of proteins and peptides molecules.Drug is administered by ethosomes in the form of gel and cream for patient comfort.

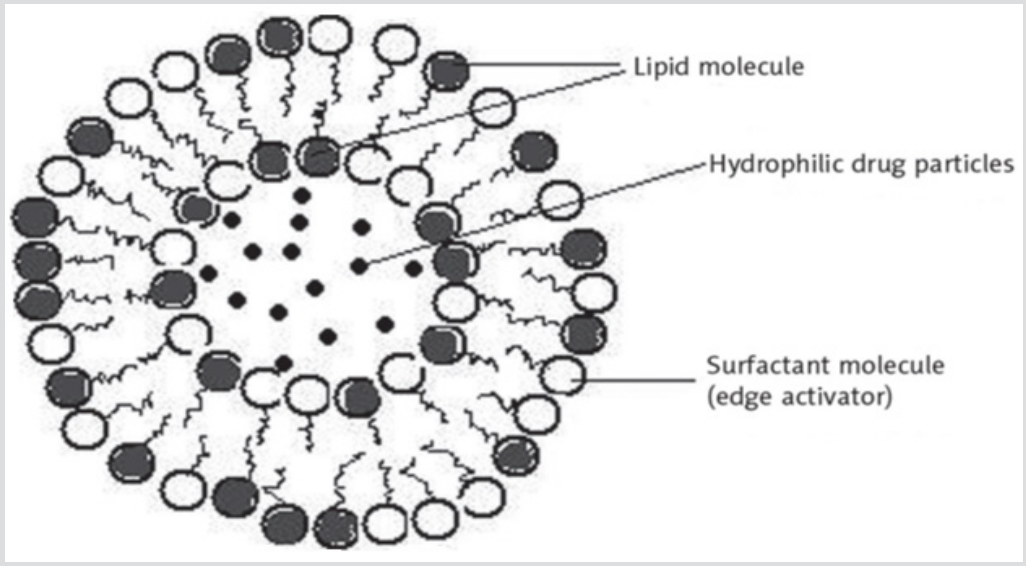


Fig 5. Structure of transferosomes

Table 5. Transferosomes herbal formulations

| S.No. | Formulations | Active ingredients | Applications | Biological activity | Route of administration |
|---|---|---|---|---|---|
| 1 | Capsaicin transferosomes | Capsaicin | Increase skin penetration | Analgesic | Topical |
| 2 | Colchicine transferosomes | Colchicine | Increase skin penetration | Antigout | In vitro |
| 3 | Vincristine transferosomes | Vincristine | Increase entrapment efficiency and skin permeation y | Anticancer | In vitro |

Table 6.Ethosomes formulations

| S.No. | Formulations | Active ingredients | Applications | Biological activity | Route of administration |
|---|---|---|---|---|---|
| 1 | Matrine ethosome | Matrine | Improve the percutaneous permeation | Anti-inflammatory | Topical |
| 2 | Ammonium glycyrrhizinate ethosomes | Ammonium glycyrrhizinate | Increase of the in vitro percutaneous permeation | Anti-inflammatory | Topical |

## 2.7. MICROSPHERES

Microsphere comprises of small spherical particles, with diameters in the micrometer range, typically 1 μm to 1000 μm (1 mm). Microspheres are sometimes referred to as micro-particles, they are classified as biodegradable or non-biodegradable[28].

Biodegradable microspheres include albumin microspheres, modified starch microspheres, gelatin microspheres, polypropylene dextranmicrospheres, polylactic acid microspheres, etc. According to the current literature reports on non-biodegradable microspheres, polylactic acid is the only polymer approved to be used by people, and it is used as a controlled-release agent. Solid and hollow microspheres vary widely in density and therefore are used for different applications.

Hollow microspheres are typically used as additives to lower the density of a material. In addition, reports on immune microsphere and magnetic microsphere are also common in recent years. Immune microsphere possesses the immune competence as a result of the antibody and antigen being coated or adsorbed on the polymer microspheres[29].

Administration of medication via micro particulate systems is advantageous because microspheres can be ingested or injected and; they can be tailored for desired release profiles and used site-specific delivery of drugs and in some cases can even provide organ-targeted release. So far, a series of plant active ingredients, such as rutin, camptothecin, zedoary oil, tetrandrine, quercetine and Cynara scolymus extract has been made into microspheres (Table no.7). In addition, reports on immune microsphere and magnetic microsphere are also common in recent years. Immune microsphere possesses the immune competence as a result of the antibody and antigen was coated or adsorbed on the polymer microspheres[30].

## 2.8 Transdermal Drug Delivery System (Transdermal Patches)

Transdermal drug delivery system involves non-invasive delivery of the medication from the surface of skin, through its layers, to the circulatory system. Medication delivery is carried out by a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. A transdermal patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into bloodstream[31].

## 3. PROPRIETARY NOVEL DRUG DELIVERY SYSTEM OF PLANT ACTIVES AND EXTRACTS

Cosmetochem International AG is a Swiss-based company, specialized in the production of high quality, customized botanical extracts and actives launch botanical, standardized, liposomal powders named Liposome Herbasec® a novel range of standardized botanical extracts in a liposomal-based powder form[32]. As the liposome carriers are very effective penetration enhancers which serve as carriers to the skin, increasing the bioavailability of the plant extracts. In present formulation the freeze-dried dispersion of Liposome Herbasec® is reformed when dispersed in water, re-encapsulating the concentrated plant extract[33]. Phospholipids used for the preparation of formulation are the safest, mildest substances which allow the penetration of the plant actives into the deeper layers of the epidermis and avoid the use of solvents[34].

A Phytosome® is generally more bioavailable than a simple herbal extract due to its enhanced capacity to cross the lipid-rich biomembranes and reach circulation[35]. To overcome the poor bioavailability of silybin, Indena has complexed it with soy phospholipids exploiting the Phytosome® technology[36]. As demonstrated by comparative pharmacokinetic studies, Silipide® represents the most absorbable oral form of silybin known. The pharmacokinetics of Silipide® in healthy human subjects showed that complexation with phosphatidylcholine improved the oral bioavailability of silybin 4.6 fold compared with silymarin, presumably because of a facilitated passage across the gastrointestinal mucosa[37]. The good bioavailability of Siliphos® was confirmed in a human pharmacokinetic study in prostate cancer patients. The study employed

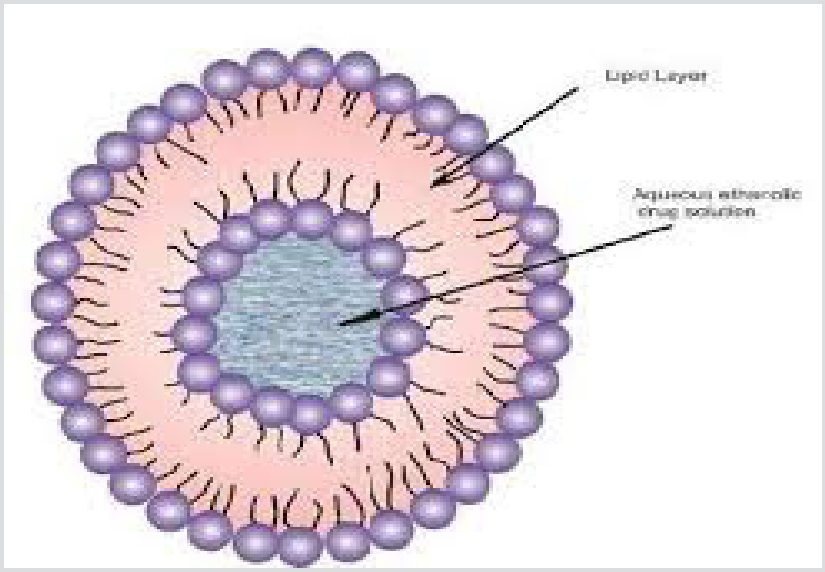


Fig 6. Structure of ethosome

Table 7.Microspheres encapsulated herbal formulations

| S.No. | Formulations | Active ingredients | Applications of formulations | Biological activity | Route of administration |
|---|---|---|---|---|---|
| 1 | Rutin–alginate–chitosan microcapsules | Rutin | Targeting into cardiocascular and cerebrovascular region | Cardiovascular and Cerebrovascular diseases | In vitro |
| 2 | Zedoary oil microsphere | Zedoary oil | Sustained release and Higher bioavailability | Hepatoprotective | Oral |
| 3 | CPT loaded microspheres | Camptothecin | Prolonged-release of camptothecin | Anticancer | Intraperitoneally and intravenously |
| 4 | Quercetin microspheres | Quercetin | Significantly decreases the dose size | Anticancer | In vitro |
| 5 | *Cynara scolymus*microspheres | *Cynara scolymus*extract | Controlled release of neutraceuticals | Nutritional supplement | Oral |

high dosages, and was aimed at getting information on toxicity and phase II dosage of the product[38]. Siliphos® at a daily oral dose of 13 g in 3 divided doses, was well tolerated in all patients, and this dosage was recommended for the phase II study.The results, including the optimal tolerability obtained in these "extreme" clinical situations, provide strong support for the use of Siliphos® also in less severe pathologies associated with liver damage[39]. Ginkgoselect® Phytosome® was administered at a dosage of 360 mg/day (120 mg three times per day) to 22 subjects affected by the Raynaud's disease in a double-blind, placebo-controlled trial[40]. Patients were required to record the frequency and duration of any vasospastic attack, also completing a scoring scale of the overall perception of the severity of the episodes. Patients were reviewed after two, four and ten weeks of treatment. This pilot study showed the efficacy of Ginkgoselect® Phytosome® in promoting a clear and highly statistically significant reduction in the frequency (56%) and severity of Raynaud's attacks per day. Meriva® is a patented complex of curcumin, a dietary phenolic, with soy phosphatidylcholine[41]. A lot of work that has been published in the journal Cancer Chemotherapy and Pharmacology demonstrated Meriva®'s superior bioavailability compared to a standardized curcumin extract in rats, while very promising initial preclinical results in terms of improved hydrolytical stability and human pharmacokinetics have been shown more recently[42]. Including the advantages of these above mentioned commercialized NDDS preparation of plant actives/extracts a variety of other preparations is also available which show the remarkable advantages over pure plant actives/extracts [43].

## 4. CONCLUSION

Herbal medicine is now globally accepted as a valid alternative system of therapy in the form of pharmaceuticals and extensive research is also going on in the area of novel drug delivery and targeting for plant actives and extracts. These drugs have enormous therapeutic potential which should be explored through some value added drug delivery systems. Lipid solubility and molecular size are the major limiting factors for drug molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytomolecules, despite having excellent bio-activity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. Such problems in the research, production and application need to be solved. In addition, more attention should be paid to the research on the carrier materials in order to develop more suitable carriers which can reduce the toxicity of drugs, enhance their activity and improve the overall quality of the agents. Hence there is a great potential in the development of novel drug delivery systems for the plant actives and extracts.

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