

Recent development in novel drug delivery systems of herbal drugs

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Novel technologies have been developed recently for drug delivery systems. The use of herbal formulations for novel drug delivery systems is more advantageous and has more benefits compared to others. The use of liposome, ethosome, phytosomes, emulsion, microsphere, solid lipid nanoparticles of herbal formulation has enhanced the therapeutic effects of plant extracts. With the use of all these, targeted delivery of the formulation is achieved, due to which the formulation demonstrates effect on the site, and the bioavailability of the formulation is also increased. With these novel drug delivery systems, the actives and extracts which are used in herbal formulations demonstrate enhancement in stability, sustained release of formulation, protection from toxicity and improved therapeutic efficacy. The main purpose of developing alternative drug delivery technologies is to increase efficiency of drug delivery and safety in the process of drug delivery and provide more convenience for the patient. The present paper includes information about novel formulations of herbal formulations.

Key words: Emulsion, ethosome, herbal drugs, liposome, microsphere, nanoparticles, solid lipid nanoparticle

INTRODUCTION

New Drug Delivery Systems

The majority of the pharmaceutical products have to enter the bloodstream in order to be effective. They can be taken orally, via the intestine, by injection or infusion. In addition, there are other special methods that are grouped under the collective form 'New Drug Delivery Systems'; these include the following:

- Transdermal therapeutic system (TTS), whereby the active pharmaceutical ingredient is absorbed by the skin.
- The subcutaneous injection, whereby the drug is administered almost pain free, using injection equipment.
- 'Micronized powder', whereby a pre-determined dose of powder is inhaled into lungs (pulmonary) or over the mucosal membrane (nasal) and distributed into bloodstream.
- The MEMS syringe, which is designed to be shipped pre-loaded with a lyophilized or freeze-dried drug stored in its silicone rubber reservoir.^[1]

Targeted Drug Delivery System

Targeted drug delivery system (TDDS) is also called 'targeting drug system'. It is a new drug delivery system that makes the drugs densely gather pathological-change structures, and has an enhanced treatment effect and less toxic side effects. The drugs can enhance the strength of pharmacological action and reduce the bad reaction all over the body, for they release in the target organs.

A successful targeted drug delivery system comprises three elements:

- Orientation cumulation
- Control over drug release
- Non-toxic and biodegradable

Theoretically speaking, microsphere and nanoparticles that carry a great amount of dose and the use of biology and biodegradable materials can well control the degradation and drug release half life.

Phytosome

Phospholipids-based drug delivery system has been found promising for valuable and efficient herbal drug delivery. Complexing the polyphenolic phytoconstituents in the molar ratio with phosphatidyl choline results in a new herbal drug delivery system, known as "Phytosome". It is the phytolipids delivery system which forms a bridge between the convectional delivery system and novel delivery system. The term Phytosome relates to "phyto", which means plant; while "some" means cell-like, often referred to as herbosome in certain literature.

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Phytosomes are advanced forms of herbal products that are better absorbed, utilized to produce better results than those produced by conventional herbal extracts. Phytosomes show better pharmacokinetic and therapeutic profiles than conventional herbal extracts. Phytosomes are prepared by complexing the polyphenolic phytoconstituents in the ratio of 1:2 or 1:1 with phosphatidyl choline. Most of the phytosomal studies are focused on *Silybum marianum*, which contains premier liver-protectant flavonoids. The fruit of the milk thistle plant (*S. marianum*, family: Asteraceae) contains flavonoids known for their hepatoprotective effects.^[2] The Phytosome protects herbal extract components from destruction in digestive secretions and gut bacteria by forming little cell, which is capable of being transferred from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and finally reaching blood. Various Phytosome herbal formulations are shown in Table 1.

Advantages of phytosome formulation

1. It is able to permeate the hydrophilic botanical extract to be better absorbed in intestinal lumen.
2. Phytosome increases the absorption of active constituents, so its dose size required is small.
3. There is appreciable drug entrapment and improvement in the solubility of bile to herbal constituents, and it can target the liver.
4. In Phytosome, chemical bonds are formed between phosphatidylcholine molecules, so it shows good stability.
5. Phytosome improves the percutaneous absorption of herbal phytoconstituents.^[3,4]

Liposomes

Liposomes are concentric bi-layered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bi-layer mainly composed of natural or synthetic phospholipids. The liposomes are spherical particles that encapsulate the solvents which are freely floating in the interior. Liposomes are constructed of phospholipids, which are amphipathic molecules as they have both hydrophobic tail and hydrophilic polar head as

shown in Figure 1.^[12] The polar end is composed of molecules, is phosphoric atom-bound to a water soluble molecule.

Liposomes can encapsulate both hydrophilic and lipophilic materials. Liposome has properties that enable it to enhance the ingredient solubility, bioavailability, bio-distribution, altered pharmacokinetics and *in vitro* and *in vivo* stability. Liposome drug delivery systems can enhance the therapeutic efficacy of drugs^[13] – in this connection, to improve the bioavailability of silymarin through its incorporation in a stable liposomal buccal dosage form, using commercially available soybean lecithin. A variety of herbal liposomal formulations have been studied, which are summarized in Table 2.

Advantages of liposome formulation

1. Liposome is used for drug delivery systems due to its unique structural properties.
2. Liposome can carry both the hydrophobic and hydrophilic drug. Therefore, liposome as a drug carrier can indiscriminately deliver drugs through the cell membrane.
3. Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene.
4. Liposome formulation can produce sustained and

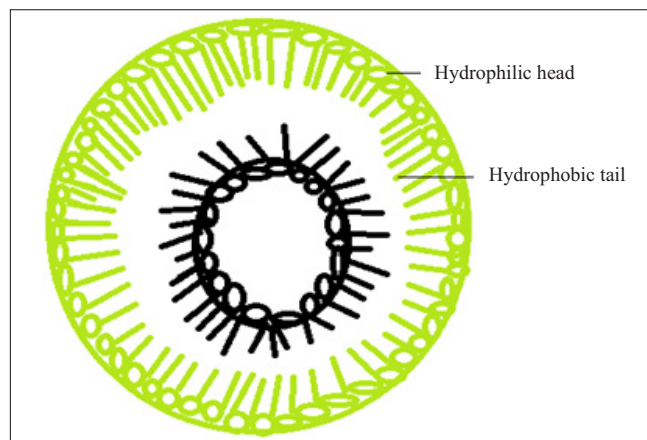


Figure 1: The liposome structure

Table 1: Herbal phytosome formulation

Active ingredients	Biological activity	Applications of phytosome formulations	Reference
Quercetin	Antioxidant activity	Enhanced therapeutic efficacy	[5]
Oxymatrine	Anti-viral	Improvement of bioavailability	[6]
Ginkgo biloba	Cardioprotective, anti-asthmatic and anti-diabetic	Induced hepatoprotective effect	[7]
Marsupium	Anti-viral	Increase in bioavailability	[8]
Embelin	Antibacterial and anti-fertility activities	Increase in solubility	[9]
Naringenin	Anti-inflammatory, anti-carcinogenic and anti-tumour effects	Increase in bioavailability; prolong the duration of action	[10]
Silybin	Hepatoprotective and antioxidant	Increase in therapeutic effect	[11]

controlled release of formulation and enhances the drug solubility.

Example of marketed liposome formulation

Liposomal herbal hair treatment preparation: A preparation of arboretum skin care formulation for nutrition and moisturizing of the scalp and prevention of hair loss. It has the following ingredients:

Extract of nettle, burdock root, white onion, birchbark, oak bark, St. John's wort, red pepper, sea kelp, chamomile, lemon, castor oil, lecithin, liposome, xanthan gum, vitamins A and E, essential oil of sage, lavender and palmarosa.

This rich herbal treatment supplies necessary nutrients to the scalp and hair roots, moisturizing and strengthening them, and promotes new hair growth. It contains beneficial vitamins and herbal and marine extracts, which are carried deep by the liposome. It is an advanced delivery system.

Nanoparticles

Nanoparticles are nano- or sub-nano-sized structures composed of synthetic or semi-synthetic polymers. In recent times, nanoparticles of herbal medicines have attracted much attention. Nanoparticles are colloidal systems with particles varying in size from 10 nm to 1000 nm. It is an effective system as the formulation is encapsulated in it easily and can easily reach the effective site. The nanospheres are the solid-core spherical particulates which are nano-metric in size. They contain drug embedded in the matrix or absorbed onto the surface; and the nanocapsules have a vesicular system, in which the drug is essentially encapsulated within the central volume surrounded by embryonic

continuous polymeric sheath.^[21] The nanoparticulate system of formulation shows advantage, as its solubility is increased and the drug can reach the target site, as compared to other systems. Microencapsulation of herbal extract in nanoparticulate is an effective way used to protect drug or food ingredients against deterioration, volatile losses, or premature interaction with other ingredients. The advantages of the nanoparticle are that it improves the absorbency of the herbal formulation, reduces the dose of formulation and increases its solubility.^[22] Various nanoparticle herbal formulations are summarized in Table 3.

Advantages of herbal nanoparticle delivery system

1. Nanoparticulate system delivers the herbal formulation directly to the site of action.
2. Encapsulating drugs within nanoparticles can improve the solubility and pharmacokinetics of drugs.
3. Nanoparticles can also reach the choice of formulations, promote the drugs through the biological barriers and increase the bioavailability of drugs.
4. It can take the drug directly to the site of action without destroying surrounding environment.

Emulsions

Emulsion is a biphasic system in which one phase is intimately dispersed in the other phase in the form of minute droplets ranging in diameter from 0.1 µm to 100 µm. In emulsion, one phase is always water or aqueous phase, and the other phase is oily liquid, i.e., non-aqueous. Among them, the micro-emulsion is also called nanoemulsion, and the sub-micro-emulsion is also called lipid emulsion. Emulsion drug delivery system is targeted or distributed well due to affinity to lymph. Micro-emulsions are solutions

Table 2: Herbal liposomal formulations

Active ingredients	Biological activity	Applications of liposome formulations	Reference
Magnolol	Inhibiting vascular smooth muscle cells (VSMCs) proliferation	Enhance the therapeutic efficacy	[14]
Nux vomica	Anti-tumour, analgesic and anti-inflammatory Activities	Increase stability of formulations	[15]
Quercetin	Antioxidant activity	Enhance therapeutic efficacy	[16]
Diospyrin	Anti-cancer activity	Enhancement of its anti-tumour effect	[17]
Myrtus communis	Antioxidant and antimicrobial activity	Increase in its activities	[18]
Artemisia arborescens	Antiviral activity	Increase in antiviral activity and stability	[19]
Puerarin	Anti-arrhythmia activity	These formulations modify their surface charge and membrane integrity	[20]

Table 3: Herbal nanoparticulate formulations

Active ingredients	Biological activity	Applications of nanostructure formulations	Reference
Berberine	Anti-neoplastic activity	<i>H. pylori</i> growth inhibition	[23]
Quercitrin	Antioxidant	Better therapeutic for intestinal anti-inflammatory	[24]
Hypocrellins	Antiviral activity	Improved performance in both stability and hydrophilicity	[25]
Silybin	Anti-hepatotoxic activity	Shows sustained release and targeting system	[26]
Ginseng	Antioxidant activity	Improvement in stability and improvement in its action	[27]
Radix salvia miltiorrhiza	Anti-angina activity	Improve bioavailability	[28]
Paclitaxel	Anti-tumour activity	Show sustained release	[29]

containing nanometre-sized droplets of an immiscible liquid dispersed in an aqueous buffer. The droplets are coated with a surfactant to reduce the surface tension between the two liquid layers. Micro-emulsion (ME) is a clear, thermodynamically stable, isotropic mixture of oil, water and surfactant, frequently in combination with a co-surfactant. In addition, emulsions produce targeted sustained release, improve the penetrability of drugs into the skin and mucous and reduce the drugs' stimulus to tissues. Various emulsion-based herbal formulations are shown in Table 4.

Advantages of emulsion-based formulations

1. It 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.
2. As a result of the lipophilic drugs being made into o/w/o emulsion, the droplets of oil are phagocytosed by macrophages and increase its concentration in liver, spleen and kidney.
3. As the emulsion contains herbal formulation, it will increase the stability of hydrolyzed formulated material and improve the penetrability of drug into skin and mucous. The new type, viz., Elemenum emulsion, is used as an anti-cancer drug and causes no harm to the heart and liver.^[30]

Microsphere

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. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Microspheres are classified as biodegradable or non-biodegradable. 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.^[38] Various herbal microsphere formulations are shown in Table 5.

Advantage of microsphere formulation

1. Administration of medication via micro-particulate system is advantageous because microspheres can be ingested or injected, and they can be tailored for desired release profiles and used for site-specific delivery of drugs and in some cases can even provide organ-targeted release.
2. Drug can be easily released from the formulation.
3. It can protect the specific function of drugs, and can release the drugs into an outer phase for a long period.

Ethosome

Ethosomes are phospholipids-based elastic nano-vesicles 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. It enables drugs to reach the deep skin layers and/

Table 4: Herbal emulsion formulations

Active ingredients	Biological activity	Applications of emulsion formulations	Reference
Azadirachta indica	Acaricidal, anti-fungal, antibacterial activities	The formulation has low toxicity	[31]
Matrine	Antibacterial, anti-inflammatory, anti-viral	Sustained-release formulation	[32]
Berberine	Anti-neoplastic activity	Sustained-release formulation	[33]
Rhubarb	Cathartic and laxative activity	Analysis of nine anthraquinones and bianthrone in rhubarb	[34]
Docetaxel	Anti-cancer activity	Increase in the residence time	[35]
Quercetin	Antioxidant	Enhance penetration into stratum corneum and epidermis	[36]
Silybin	Hepatoprotective	Sustained-release formulation	[37]

Table 5: Microsphere herbal formulations

Active ingredients	Biological activity	Application of microsphere formulations	Reference
Ginsenoside	Anti-cancer activity	To enhance solubility and stability	[39]
Quercetin	Antioxidant and anti-inflammatory activities	Enhancing its bioavailability and sustain release the formulation	[40]
Zedoary oil	Hepatoprotective	Sustained-release and higher bioavailability	[41]
Rutin	Cardiovascular and cerebrovascular diseases	Targeting into cardiovascular and cerebrovascular regions	[42]

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.^[43] For the delivery of diverse group of proteins and peptides molecules, ethosomes are preferable. Drug is administered by ethosomes in the form of gel, cream for patient comfort. Ethosomal herbal formulations are shown in Table 6.

Advantages of ethosomal drug delivery

1. Ethosomes enhance transdermal permeation of drug through skin.
2. Ethosomes are a platform for the delivery of large amounts of diverse groups of drugs.
3. The ethosomal drug is administered in semisolid form, resulting in improved patient compliance.^[43,44]

Solid lipid nanoparticles

It is a technique developed in the 1990s. It is a colloidal carrier used especially for the delivery of lipophilic compounds. It is prepared by different methods – the homogenization and the warm micro-emulsion. The average mean size of solid lipid nanoparticles ranges from 50 nm to 1000 nm. Solid lipid nanoparticles are composed of lipid matrix, which becomes solid at room temperature and also at the body temperature.^[47] The main features of solid lipid nanoparticles (SLNs) with regard to parenteral application are the excellent physical stability, protection of incorporated labile drugs from degradation. To cross blood-brain barrier, it should be made for selection of lipids and surfactants. The SLNs are prepared by different methods such as homogenization and the warm micro-emulsion high-speed stirring ultrasonication and solvent-diffusion method. Lipids show compatibility with lipophilic drugs and increase the entrapment efficiency and drug-loading into the SLN.^[48] A variety of SLN herbal formulations are shown in Table 7.

Advantages of SLN herbal formulation

1. It provides controlled release and site-specific drug targeting.
2. Large-scale production can be done.
3. In this formulation, both lipophilic and hydrophilic drugs can be loaded.

4. Another advantage is that it is made of lipid matrix (physiological lipids), which decreases danger of chronic and acute toxicity.

Controlled Drug Delivery System

Herbal gastrointestinal controlled drug delivery dosage forms including pellets and process for their preparation described is novel oral dosage form for administration of an herbal extract and process for preparing the same, wherein a herbal extract is coated on pellets and the said pellets are either filled into a capsule or compressed into a tablet. The said capsule may contain pellets coated with one or more herbal extracts, and the said tablet is compressed from pellets coated with at least two or more herbal extracts. The pellets coated with herbal extract are finally coated with a controlled-release coat of polymer, which results in controlled release of the herbal extracts into the gastrointestinal tract.^[51]

Example of marketed preparations

Ocusert

Ocusert is a long-acting sustained-delivery system used as ocular insert for the treatment of open-angle glaucoma. Ocusert consists of pilocarpine as miotic drug. Pilocarpine is obtained from the leaves of *Pilocarpus microphyllus* and other species. A soft contact lens soaked in pilocarpine solution also provides sustained delivery.

Some other examples of marketed herbal preparations are –

- Hair-growth herbal spray: Hair-growth herbal spray contains pure, natural traditional Chinese medicine including ginseng extract, Chinese angelica extraction, and *Polygonum multiflorum* extraction. It is made with efficient active constituent extracted by advanced super-critical fluid-extract (SFE) technology with high-tech bioengineering CO₂ super-critical fluid. Hair-growth herbal spray contains pure, natural TCM enhancer *Angelica naphtha*, and its functions are –
 - Influence the keratoderma hydration
 - Dissolve sebum within sebaceous gland duct
 - Enhance the entry of drugs into skin by a mechanism which includes enlarging the openings of sweat glands and purse hair follicles and make drugs

Table 6: Herbal ethosomal formulations

Active ingredients	Biological activity	Application of ethosomal formulations	Reference
Sophora Alopucuroides	Anti-endotoxic, anti-cancer and anti-inflammatory	Ethosome enhances delivery of drugs through the stratum corneum barrier into the deep layer of the skin.	[45]
Matrine	Antibacterial, anti-inflammatory, anti-rheumatism and anti-tumour	Increase the per cutaneous permeation and improve anti-inflammatory effect	[46]

Table 7: SLN herbal formulations

Active ingredients	Biological activity	Applications of SLN herbal formulations	Reference
Curcumin	Anti-tumour, antioxidant and anti-inflammatory activities	Increase in stability	[49]
Curcuminoids	Anti-malarial activity	Increase in activity	[50]

enter hair follicles to the greatest extent; improving the scalp blood circulation; making sebaceous gland unhindered; restoring the hormone secretion level; and balancing the immune system.

- Offer abundant aminophenol; metallic elements, including Cu and Fe; and nutrition, including vitamins B₁, B₂, B₃, for hair growth, activating the regeneration of hair follicles and solving the problem of hair loss.

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.^[52]

Some examples of marketed preparations

- a. The virility patch: The virility patch (RX male virility enhancement formula) is a natural herbal patch containing a variety of herbs known for promoting sexual desire and performance in men. The virility patch is an ultra-concentrated formula infused into a small, discrete dermal patch which sticks to the body. Like other patches, such as nicotine patch and other diet patches, these products use advanced physiological technology to feed the formulation into user's bloodstream in a timely manner. The patch's potent blend of ingredients is instantly absorbed into the skin. The advantage is that the product does not need to travel to the digestive system and it begins working immediately for fast and effective virility enhancement. The transdermal delivery system used in these patches is approved by the FDA.^[52,53]
- b. Transdermal slimming patch (Levin Health Care): It is entirely made of natural herbs and processed to soft patch form with transdermal technology. This reduces the overburden of vital organs. It works 24 hours — all day, all night. It eliminates hunger pangs, maintains the feeling of fullness, even when one has not eaten, and accelerates fat burning.

Mode of action: Pristine slimming patch has dual action.

- It creates in stomach a sensation of fullness before eating, and extra food is not required.
- It is also a metabolic accelerator, i.e., stored fat; the pristine slimming patch helps to eat slightly less food.

Ingredients: The pristine slimming patch is infused with a powerful proprietary blend of herbs for suppressing appetite and increasing energy and metabolism. Various ingredients are —

- Fucus vericulosus: Burns fat, up the metabolic breakdown fatty tissues. It is approved by the UK Medicine Control Agency.
 - Guarana: It is a climb shrub that is grown in the Amazon region of Brazil and Uruguay. It increases mental alertness, fights fatigue, slows the pulse and decreases appetite.
 - 5-HTT: Enhances weight loss by preventing dieting-associated decline in serotonin.
 - Zinc pyruvate: Enhances fat burning. Decreases blood glucose and lowers blood cholesterol.
 - Flaxseed oil: Keeps balance of essential fatty acids for healthier dieting.
 - Lecithin: Helps breakdown fats/cholesterol. Prevents arterial congestion.
 - L-Carnitine: Facilitates the burning of fat for energy.
 - Zinc citrate: An essential mineral, often lost when losing weight.^[53]
- c. The Health Technology Assessment (HTA) Review covers the use of nicotine replacement therapy (NRT) as “cut down to quit” (CDTQ) agent, rather as a complete replacement for nicotine from tobacco. CDTQ is also known as “reduce to stop”. NRT is obtained in gum or inhalators (the two forms recognized by the new UK license for CDTQ). NRT is also available as transdermal patch. CDTQ is a new designation for nicotine replacement therapy.^[54]

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