

NOVEL DRUG DELIVERY SYSTEM IN HERBAL'S

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ABSTRACT

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. 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 polyhedral systems. Determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) Of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposome, solid lipid nanoparticles and so on. The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. Many herbal compounds including quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside have demonstrated capability to enhance the bioavailability.

1. INTRODUCTION

To minimize drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability and the fraction of the drug accumulated¹.

1.1 Novel drug delivery system

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated².

A novel drug delivery system is a system that offers multiple drug delivery solutions such as⁶

1. Oral Drug Delivery Systems and Materials.

2. Parenteral and Implant Drug Delivery Systems.
3. Pulmonary and Nasal Drug Delivery.
4. Transmucosal Drug Delivery.
5. Transdermal and Topical Drug Delivery.
6. Delivery of Proteins and Peptides.
7. Drug Delivery Pipelines.
8. Drug Delivery Deals.

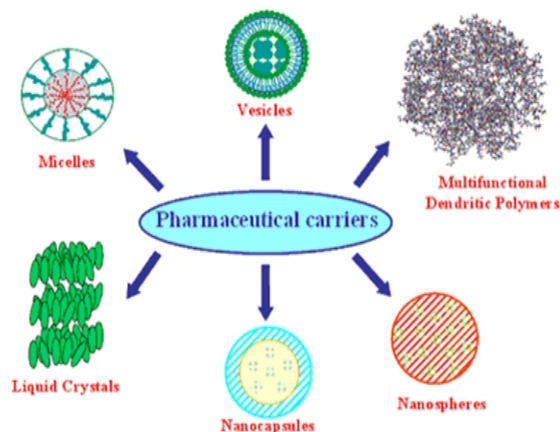


Fig. 1.1: Pharmaceutical carriers

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Modern medicine cures a particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.²

1.2 Types of novel drug delivery systems⁶

1. Sublingual that is, a drop under the tongue.
2. Self adhesive patch on skin.
3. Pump e.g. Insulin pump.
4. Special pervious plastic injected below skin e.g. Norplant.

1.3 Recent developments

In the recent years, nanostructured carrier system like polymeric nanoparticles, liposomes, SLNs, polymeric micelles, nanoemulsions, etc., have been investigated for their potential to deliver anticancer drugs by oral route. Moreover, the oral route offers great potential for delivery of cytotoxic agents and therefore the attention has focused on the development of oral chemotherapy in oncology.

1.4 recent developments in novel drug delivery system of herbals⁶

- 1.4.1 Phytosome
- 1.4.2 Liposome
- 1.4.3 Nanoparticles
- 1.4.4 Emulsions
- 1.4.5 Microsphere
- 1.4.6 Ethosome
- 1.4.7 Solid lipid nanoparticle
- 1.4.8 Controlled Drug Delivery System
- 1.4.9 Other novel vesicular herbal formulations
- 1.4.10 Proprietary novel drug delivery system of plant actives and extracts
- 1.4.11 Niosomes
- 1.4.12 Proniosomes
- 1.4.13 Transdermal Drug Delivery System
- 1.4.14 Dendrimers
- 1.4.15 Liquid Crystals
- 1.4.16 Hydrogels

1.4.1 phytosome

Phospholipids-based drug delivery system has been found promising for valuable and efficient herbal drug delivery.⁷Complexing the polyphenolic phytoconstituents in the molar ratio with phosphatidyl choline results in a new herbal drug delivery system, known as "Phytosome".⁸ Most of the phytosomal studies are focused on *Silybummarianum*, which

contains premier liver-protectant flavonoids. The fruit of the milk thistle plant (*S. marianum*, family: Asteraceae) contains flavonoids known for their hepatoprotective effects⁹.

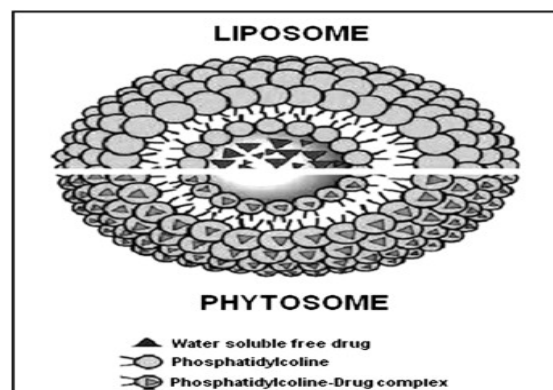


Fig. 1.2: Difference between liposome and phytosome

Advantages of phytosome formulation

1. Phytosome increases the absorption of active constituents, so its dose size required is small.
2. There is appreciable drug entrapment and improvement in the solubility of bile to herbal constituents, and it can target the liver.
3. In Phytosome, chemical bonds are formed between phosphatidylcholine molecules, so it shows good stability¹⁰.
4. Phytosome improves the percutaneous absorption of herbal phytoconstituents¹².

1.4.2 liposome

Liposome is concentric bi-layered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bi-layer mainly composed of natural or synthetic phospholipids⁸. The liposome is spherical particles that encapsulate the solvents which are freely floating in the interior. The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse (float) into their interior¹¹.

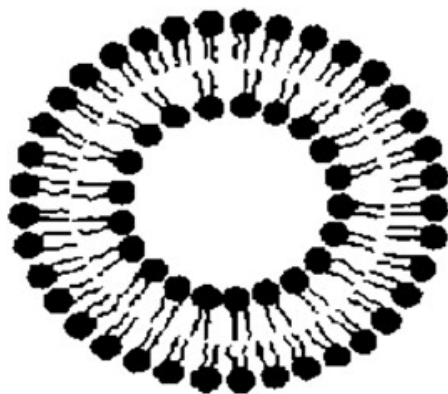


Fig. 1.3: Cross-section of a liposome

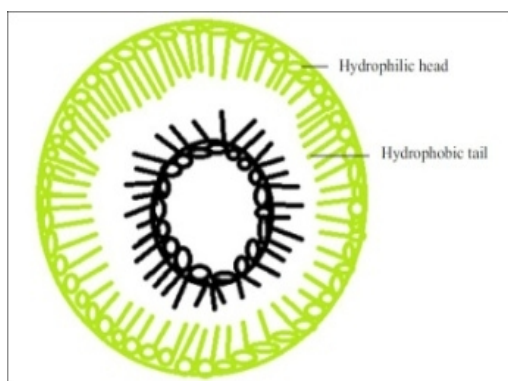


Fig. 1.4: The liposome structure

Advantages of liposomes

1. The high biocompatibility.
2. The easiness of preparation.
3. The chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds.
4. The simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components.

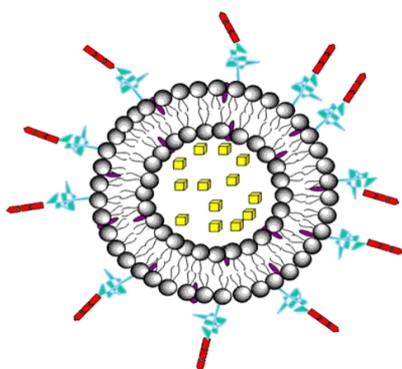


Fig. 1.5: Drug encapsulation in liposomes

1.4.3 nanoparticles

Nanoparticles are nano- or sub-nano-sized structures composed of synthetic or semi-synthetic polymers.² 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. 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 ingredients¹².



Fig. 1.6: Nanoemulsion

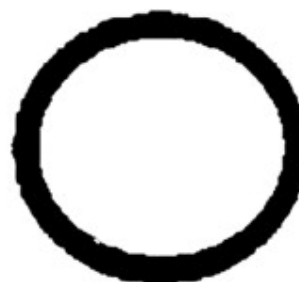


Fig. 1.7: Biopolymeric nanoparticle

Advantages of herbal nanoparticle delivery system

1. Nanoparticulate system delivers the herbal formulation directly to the site of action.
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Improved pharmacokinetic effect.
5. Producible with various sizes, compound surface properties.

Disadvantages

1. Include their tendency to be taken up by cells of retico-endothelial system and the slow release of the drug when the liposomes are taken up by phagocytes

through endocytosis, fusion, surface adsorption or lipid exchange.

2. Stabilizing the formulated liposomes is also difficult, but many approaches are now used for their stabilization.

1.4.4 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 called lipid emulsion¹³. Micro-emulsion (ME) is a clear, thermodynamically stable, isotropic mixture of oil, water and surfactant, frequently in combination with a co-surfactant¹⁴.

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.

1.4.5 Microsphere

Microsphere comprises of small spherical particles, with diameters in the micrometer range, typically 1 μm to 1000 μm (1 mm). Glass microspheres, polymer microspheres and ceramic microspheres are commercially available.¹³ Microspheres are classified as biodegradable or non-biodegradable. Biodegradable microspheres include albumin microspheres, modified starch microspheres, gelatin microspheres, polypropylene dextran microspheres, polylactic acid microspheres, etc¹⁵.

Advantages of microsphere formulations

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.

1.4.6 Ethosome

Ethosomes are phospholipids-based elastic nano-vesicles having high content of ethanol (20%-45%). 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/ or systemic circulation¹⁶.

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.

1.4.7 Solid lipid nanoparticle

It is a technique developed in the 1990s. It is a colloidal carrier used especially for the delivery of lipophilic compounds. 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 at the body temperature¹⁷.

Advantages of SLN herbal formulation¹²

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.

1.4.8 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 tablet¹⁸.

1.4.9 Other novel vesicular herbal formulations

Transferosomes are applied in a non-occluded method to the skin, which permeate through the stratum corneum lipid lamellar regions because of the hydration or osmotic force in the skin. It can be applicable as drug carriers for a range of small molecules, peptides, proteins and herbal ingredients which shows the better topical absorption in comparison to pure capsaicin. Ethosome, as a novel liposome, is especially suitable as a topical or transdermal administration carrier¹⁹.

1.4.10 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 form¹⁹.

1.4.11 Niosomes

Niosomes are multilamellar vesicles formed from non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol. Earlier studies, in association with L'Oreal have shown that, in general, niosomes have properties as potential drug carriers similar to liposomes. Niosomes are different from liposomes in that they offer certain advantages over liposomes¹¹.

1.4.12 Proniosomes

Proniosome gel system is step forward to niosome, which can be utilized for various applications in delivery of actives at desired site. Proniosomal gels are the formulations, which on in situ hydration with water from the skin are converted into niosomes¹³.

1.4.13 Transdermal drug delivery system

Transdermal drug delivery system has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. But immense potential lies in transdermal drug as future smart drug delivery devices¹⁸.

1.4.14 Dendrimers

Dendrimers are nanometer-sized, highly branched and monodisperse macromolecules with symmetrical architecture. While their stability and protection from the Mononuclear Phagocyte

System (MPS) is being achieved by functionalization of the dendrimers with polyethylene glycol chains (PEG)⁶.

1.4.15 Liquid crystals

Liquid Crystals combine the properties of both liquid and solid states. They can be made to form different geometries, with alternative polar and non-polar layers (i.e., a lamellar phase) where aqueous drug solutions can be included¹⁹.

1.4.16 Hydrogels

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. They are used to regulate drug release in reservoir-based, controlled release systems or as carriers in

swellable and swelling-controlled release devices².

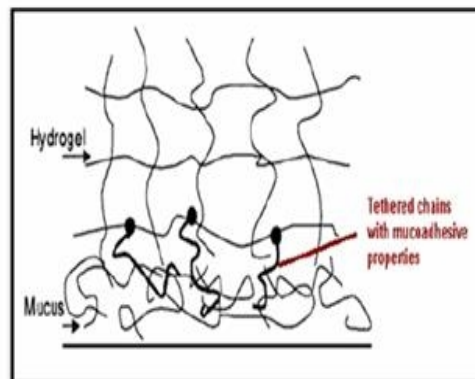


Fig. 1.8: Pegylated and pH sensitive micro- or nanogels

1.5 Advantage of novel drug delivery system³

1. Protection from physical and chemical degradation.
2. Sustained delivery.
3. Improved tissue macrophages distribution.
4. Enhancement of stability.
5. Enhancement of pharmacological activity.
6. Protection from toxicity.
7. Increased bioavailability.
8. Enhancement of solubility.

1.6 advantage of herbal drug³

1. Longer duration of treatment.
2. Lack of regulation.
3. Poison risk associated with wild herbs
4. Lack of dosage instruction.
5. Not suitable for many disease.
6. Limitation of Herbal drug.
7. Widespread availability.
8. Lower cost.
9. More effectiveness.
10. Low risk of side effect.

2. HERBS USED AS NOVEL DRUG DELIVERY SYSTEM

2.1 herbal drugs

Herbal formulation a dosage form consisting of one or more herbs or processed herb in specified quantities to provide specific nutritional, cosmetic benefits, and other benefits meant for use to diagnose treat or to alter the structure or physiology of human beings or animals. Herbal preparations are obtained by subjecting whole plants, fragmented or cut plants, plants part to treatment such as extraction, distillation, expression fractionation, purification, concentration or fermentation. This

includes comminuted or powdered herbal substances, extract. Essential oils, expressed juices etc²⁰. Many herbal drugs and herbal extracts despite of their extraordinary potential *in-vitro* finding, demonstrate less or no *in-vivo* actions due to their poor lipid solubility or improper molecular size or both, ultimately resulting in poor absorption and poor bioavailability²¹. Phytochemical and phytopharmacological studies have long been established overall health boosting capacities of various plant products but there is a great interest and medical need for the improvement of bioavailability of a large number of herbal drug and plant extract which are poorly lipid soluble and so are less bioavailable²¹.

2.2 herbal novel drug delivery systems

As herbal novel drug delivery systems have lot of potential, several researchers are working towards developing novel drug delivery systems like mouth dissolving tablets, sustained and extended release formulations, mucoadhesive systems, transdermal dosage forms, microparticles, microcapsules, nanoparticles, implants etc. of herbs. Some of them are at the laboratory stage and some have reached to the market²².

2.3 There are three main reasons for the popularity of herbal media

1. There is a growing concern over the reliance and safety of drugs.
2. Modern medicine is failing to effectively treat many of the most common health condition.
3. Many natural measures are being shown to produce better results than drugs or surgery without the side effects.

Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines.¹⁶ Phytotherapeutics need a scientific approach to deliver the components in a sustained manner to increase patient compliance and avoid repeated administration. This can be achieved by designing novel drug delivery systems (NDDS) for herbal constituents. NDDSs not only reduce the repeated administration to overcome non-compliance, but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability. Hence, integration of the nanocarriers as a NDDS in the Traditional medicine system is essential to conflict more chronic diseases like asthma, diabetes, cancer, and others²².

2.4 need for novel drug delivery system "nanocarrier" for "herbal remedies

Herbal remedies were selected as feasible drug candidate for delivery through a nano delivery system because of the following properties¹

1. Effective chloroform, petrol, acetone, and methanolic extracts are available which may not be suitable for delivery as such.
2. These are the bulk drugs so dose reduction is intended.
3. Currently marketed formulations lack target specificity for various chronic diseases.
4. Some other side effects are associated with currently marketed formulations.
5. Patient non-compliance due to large doses and less effectiveness with the available formulations.

2.5 importance of novel drug delivery systems in herbal medicines

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems²². Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. [23] If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases. 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 systems²⁴. However, modern phytopharmaceutical research can solve the scientific needs (such as determination of Pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on²⁵.

2.6 herbal plants

2.6.1 *Rauwolfia beddomei*

The instrumental in manufacturing and supplying a wide range of Herbal Extracts to our esteemed customers. We offer our range of herbal extracts is either in liquid or dry powder form. These extracts are highly acclaimed across the globe for their customized extraction as per the specifications provided by our clients²⁶.

2.6.2 *Holarrhena antidysenterica*

The rich industry experience, we have an expertise in offering a wide range of *Holarrhena Antidysenterica* Herbs. These herbs are the best cure for nervous disorders, throat infections, cough bronchitis, tuberculosis, and dyspepsia, scalding of urine, general debility and tumors. Clients can avail these herbs at affordable prices from us^{26, 27}.

2.6.3 *Aloe vera*

Biological Source

Dried juice of leaves of *Aloe vera*, *Aloe barbadensis*, and *Aloe ferox*.

Family

Liliaceae

Chemical Constituents

Amino acids, anthraquinones, enzymes, hormones, lignin, minerals, aloe emodin.

Importance

Aloe will bring cooling relief to fleabites, reducing itching and scratching and is safe to use on dogs and cats. It also has immune-stimulating and anti-inflammatory compounds. Acemannan, a chemical compound found in Aloe Vera as a powerful immunostimulant in animals, particularly in cats.

Medicinal Uses

Acne, Ayurvedic, Beauty, Burns, Constipation, Cuts Wounds, Facial Care, Analgesic, Anti-inflammatory, Antibacterial, Antifungal.^{28,29}

2.6.4 Nettle

Biological Source

Urtica dioica

Family

Urticaceae

Chemical Constituents

formic acid, mucilage, ammonia, carbonic acid, water.

Importances

Nettle is one of nature's best nutraceuticals, containing protein, calcium, phosphorus, iron, magnesium, beta-carotene, along with vitamins A, C, D, and B complex, all in a form that is easy for the body to use. Extracts of nettle roots are reliable diuretics that encourage excretion of uric acid, but simultaneously discourage nighttime bathroom urges, making this remarkable plant useful for such disparate problems as gout, and the overnight incontinence of benign prostate enlargement and weak and irritated bladder. Frequent use of nettle leaf tea, a cup or more daily, rapidly relieves and helps prevent water retention. Nettle is a superb nourisher of the kidneys and adrenals.

Medicinal Uses

Analgesic, Anodyne, AntiCancer, Astringent, Depurative, Diuretic, Tonic³⁰.

2.6.5 *Indian senna*³¹

Biological Source

Dried leaflets of *Cassia angustifolia*.

Family

Leguminosae.

Chemical Constituents

Sennosides A and B (not less than 2.5%).

Importance

Indian Senna or Tinnevely senna is a shrub very highly esteemed in India for its medicinal value. The leaves are useful in constipation, abdominal disorders, leprosy, and skin diseases, leucoderma, splenomegaly, hepatopathy, jaundice, helminthiasis, dyspepsia, cough, Bronchitis, typhoid fever, anaemia, tumours and vitiated conditions of pitta and vata. It is used in Ayurvedic preparations; "Pancha Sakara Churna", "Shat Sakara Churna" and "Madhu Yastyadi Churna" used for constipation. Its use is widespread in Unani system and some of the important products of this system containing senna are "Itrifal Mulayyin", "Jawarish Ood Mulayyin", "Hab Shabyar", "Sufuf Mulliyin", "Sharbat SAhmad Shahi", etc. used as a mild laxative³².

Medicinal Uses

purgative, irritate and stimulant the colon, therapeutic action.³¹

2.6.6 *Brahmi*

Biological Source

It is the herb of *Centella asiatica*.

Family

Umbelliferae

Chemical Constituents

Amycin, Asiatic acid, madecassic acid, isobrahmic acid, arabinose, glucose, rhamnose.

Importance

Brahmi or Thyme leaved gratiola is an important drug in Ayurveda for the improvement of intelligence and memory and revitalisation of sense organs. It clears voice and improves digestion. It is suggested against dermatosis, anaemia, diabetes, cough, dropsy, fever, arthritis, anorexia, dyspepsia, emaciation, and insanity. It dispels poisonous affections, splenic disorders and impurity of blood. It is useful in vitiated conditions of kapha and vata, biliousness, neuralgia, ascites, flatulence, leprosy, leucoderma, syphilis, sterility and general debility. The whole plant is used in a variety of preparations like Brahmi ghritam, Sarasvati rasam, Brahmi tailam, Misrakasneham, etc. In unani Majun Brahmi is considered as a brain tonic.

Medicinal Uses

Nervine tonic, sedative, spasmolytic³³.

2.6.7 Liquorice**Biological Source**

Dried, peeled, unpeeled, root and stolon of *Glycyrrhiza glabra*.

Family

Leguminosae.

Chemical Constituents: Triterpenoids saponin, glycyrrhizic acid, potassium, calcium salt, glycyrrhetic acid glucose (4%), sucrose (2.5 to 6.5%).

Importance

Liquorice or *Muleti* is a perennial herb or under shrub about 1m high. Its dried peeled or unpeeled underground stems and roots constitute the drug which is an important constituent of all cough and catarrh syrups, throat lozenges and pastilles. This has been used in medicine for more than 4000 years. Hippocrates (400 BC) mentioned its use as a remedy for ulcers and quenching of thirst. Dioscorides, the father of Greek medicine described this drug in detail and considered it useful for maintaining shape of arteries and in burning stomach, trouble of liver and kidney, scabies, healing of wounds and as a remedy for eye diseases. It has been used in Arab system of medicine for more than 600 years from where it has been adopted to Modern medicine.

Medicinal Uses

Expectorant, demulcent, cough mixture, peptic ulcer, anti-inflammatory, anti-spasmodic³⁴.

2.6.8 Indian ginseng**Biological Source**

Dried root of *panax ginseng*.

Family

Araliaceae

Chemical Constituents

Ginsenosides, panaxosides, chikusetsusaponin.

Importance

Indian ginseng or *Winter cherry* is an erect branching perennial undershrub which is considered to be one of the best rejuvenating agents in Ayurveda. Its roots, leaves and seeds are used in Ayurvedic and Unani medicines, to combat diseases ranging from tuberculosis to arthritis. The pharmacological activity of the plant is attributed to the presence of several alkaloids and withanolides. Roots are prescribed in medicines for hiccup, several female disorders, bronchitis, rheumatism, dropsy, stomach and lung inflammations and skin diseases. Its roots and paste of green leaves are used to relieve joint pains and inflammation. It is also an ingredient of medicaments prescribed for curing disability and sexual weakness in male. Leaves are used in eye diseases. Seeds are diuretic. It is a constituent of the herbal drug '*Lactare*' which is a galactagogue.

Medicinal Uses

Immunomodulatory, aphrodisiac, stimulant, sedative, adrenal & thyroid dysfunctioning³⁵.

2.6.9 Shatavari**Biological Source**

Dried root and leaves *Asparagus racemosus*.

Family

Liliaceae

Chemical Constituents

Shatavari 1-4 (0.2%), shatavari 1 contain 3 glucose & rhamnose, shatavari 4 contain 2 glucose & one rhamnose. Asparagus roots contain protein 22%, fat 6.2%, Carbohydrate 3.2%, Vitamin B 0.36%, Vitamin C 0.04% and traces of Vitamin A.

Importance

Asparagus is a climbing undershrub with widespread applications as diuretic, cooling agent and an excellent safe herbal medicine for ante-natal care. It is useful in nervous disorders,

dyspepsia, diarrhoea, tumours, inflammations, vitiated conditions of vata and pitta, burning sensation, hyperdipsia, ophthalmopathy, nephropathy, hepatopathy, strangury, Scalding of urine, throat infections, tuberculosis, cough, bronchitis, gleet, gonorrhoea, leucorrhoea, leprosy, epilepsy, fatigue, hyperacidity, colic haemorrhoids, hypertension, abortion, agalactia, cardiac and general debility (Warrier et al, 1993). Shatavari is described in Rigveda and Atharvaveda. In Ayurvedic classics it is prescribed as a cooling agent and uterine tonic.

Medicinal Uses

Galactagogue, tonic, diuretic, antioxytocic, rheumatism and nerve disorders³⁶.

3. FORMULATION /DOSAGE FORMS AVAILABLE AS NOVEL DRUG DELIVERY SYSTEM IN HERBALS

3.1 novel drug delivery system based herbal formulations

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. In phyto-formulation research, developing nano dosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes, and nanoemulsion etc.^[2]) have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection 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. Herbal preparations are obtained by subjecting whole plants, fragmented or cut plants, plant parts to treatment such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. This includes comminuted or powdered herbal substances, extract, essential oils, expressed juices etc¹⁶.

3.2 Techniques in formulation³⁷

The techniques commonly used for the formulation are

3.2.1 High-pressure homogenization method

In this method, the lipid is pushed with high pressure (100 to 2 000 bar) through a very high shear stress, which results in disruption of

particles down to the submicrometer or nanometer range. High-pressure homogenization method is a very reliable and powerful technique for the large-scale production of nanostructured lipid carriers, lipid drug conjugate, SLNs, and parenteral emulsions.

3.2.2 Complex coacervation method

This is a spontaneous phase separation process of two liquid phases in colloidal systems, which results by the interaction of two oppositely charged polyelectrolytes upon mixing in an aqueous solution.

3.2.3 Co-Precipitation method

This method is a modification of the complex coacervation method for the preparation of nanoscale core-shell particles. This method has been reported to provide good dispersion stability to poorly water-soluble drugs.

3.2.4 Salting-out method

This method is based on the phenomenon that the solubility of a non-electrolyte in water is decreased upon addition of an electrolyte.

3.2.5 Nanoprecipitation method or solvent displacement method

This method is based on interfacial deposition of a polymer after displacement of a semipolar solvent miscible with water from a lipophilic solution, thereby resulting in a decrease in the interfacial tension between the two phases, which increases the surface area with a subsequent formation of small droplets of organic solvent even without any mechanical stirring.

3.2.6 Solvent emulsification-diffusion method

The method involves preparation of an o/w emulsion using oil phase containing polymer and oil in an organic solvent, which is emulsified with the aqueous phase, containing stabilizer, in high shear mixer, followed by addition of water to induce the diffusion of organic solvent, thus resulting in formation of nanoparticles.

3.2.7 Supercritical fluid methods

This method can be used to prepare submicrometer-sized and nano-sized formulations. A supercritical fluid (SCF) can either be a liquid or gas and used above its thermodynamic critical point of temperature and pressure. The most commonly used SCFs are carbon dioxide and water.

3.2.8 Self-assembly methods

Self-assembly is the physical process wherein pre-existing disordered components, atoms, or molecules organize themselves

3.3 Formulation of NDDS in herbals

Table 3.3.1: Phytosomal herbal formulations³⁷

Formulations	Active ingredients	Applications of Phytosomal formulations	Biological activity	Method of preparation	Dose	Route of administration
Ginkgo biloba phytosomes	Flavonoids	Flavonoids of GBP stabilize the ROS	Cardio-protective, antioxidant activity	Phospholipids complexation	100 mg and 200 mg/kg	Subcutaneous
Silybin phytosome	Flavonoids	Absorption of silybin phytosome from silybin is approximately seven times greater	Hepatoprotective, antioxidant for liver and skin	Silybin-phospholipid complexation	120 mg	Oral
Ginseng phytosome	Ginsenosides	Increase absorption	Nutraceutical, immunomodulator	Phospholipids complexation	150 mg	Oral
Curcumin phytosomes	Curcumin	Increase bioavailability	Antioxidant, anticancer	Curcumin-phospholipid complexation	360 mg/kg	Oral
Grapeseed lipid based systems	Epigallocatechin	Increases absorption	systemic antioxidant	Phospholipid complexation	50-100 mg	Oral
Hawthorn lipid based systems	Procyanidins	The blood TRAPn significantly elevated	Cardio-protective and anti-hypertensive	Phospholipid complexation	100 mg	Oral
Ybin Phytosome	Flavonoids	Absorption of silybin phytosome from silybin is approximately seven times greater	Hepatoprotective, antioxidant for liver and skin	Silybinphospho lipid complexation	-	Oral
Quercetin Phytosome	Quercetin	Exerted better therapeutic efficacy	Antioxidant, Anticancer	Quercetin-phospholipid complexation		Oral
Naringenin Phytosomes	Naringenin	Prolonged duration of action	Antioxidant Activity	Naringenin-phospholipid complex		Oral

Table 3.3.2: Liposomal herbal formulation³⁸

Formulations	Active ingredients	Applications of liposome formulations	Biological activity	Method of preparation	% Entrapment efficiency	Route of administration
Liposomes encapsulated silymarin	Silymarin	Improve bioavailability	Hepatoprotective	Reverse evaporation technique	69.22 ± 0.6%	Buccal
Ampelopsin liposome	Ampelopsin	Increase efficiency	Anticancer	Film-ultrasound method	62.30%	In vitro
Curcumin liposome	Curcumin	Long-circulating with high entrapment efficiency	Anticancer	Ethanol injection method	88.27 ± 2.16%	In vitro
Garlicin liposome	Garlicin	Increase efficiency	Lungs	Reverse-phase evaporation method	90.77 % -	

Table 3.3.3: Nano structured herbal formulations³⁷

Formulations	Active ingredients	Applications of nanostructured formulations	Biological activity	Method of preparation	% Entrapment efficiency	Route of administration
Triptolide-loaded solid lipid nanoparticle	Triptolide	Decreasing the toxicity	Anti-inflammatory	Emulsification-ultrasound	-	Oral
Artemisinin nanocapsules	Artemisinin	Sustained drug release	Anticancer	Self-assembly procedure	90-93%	In vitro
Berberine-loaded nanoparticles	Berberine	Sustained drug release	Anticancer	Ionic gelation method	65.40 ± 0.70%	In vitro
Glycyrrhizic acid-loaded nanoparticles	Glycyrrhizic acid	Improve the bioavailability	Anti-inflammatory, antihypertensive	Rotary-evaporated filmultrasonication method	91.76%	-

Table 3.3.4: Emulsion herbal formulations³⁹

Formulations	Active ingredients	Applications of emulsion formulations	Biological activity	Method of preparation	Droplet size	Drug loading	Route of administration
Docetaxel submicron emulsion	Docetaxel	Improve residence time	Anticancer	High pressure Homogenization method	166.00 nm	90%	Intravenous
Berberine nanoemulsion	Berberine	Improve residence time and absorption	Anticancer	Drawing ternary phase diagram	56.80 nm	0.50%	Oral
Silybin nanoemulsion	Silybin	Sustained release formulation	Hepatoprotective	Emulsification method	21.20 nm	-	Intramuscular
Quercetin micro-emulsion	Quercetin	epidermis	Antioxidant	High speed Homogenization method	10-100 nm	0.3% solution	Topical

Table 3.3.5: Microspheres encapsulated herbal formulations³⁸

Formulations	Active ingredients	Applications of formulations	Biological activity	Method of preparation	Size in μm	Route of administration
Zedoary oil microsphere	Zedoary oil	Sustained release and Higher bioavailability	Hepatoprotective	Quasi-emulsion-solvent diffusion method	100-600	Oral
CPT loaded microspheres	Camptothecin	Prolonged-release of camptothecin	Anticancer	Oil-in-water evaporation method	10	Intraperitoneally and intravenously
Quercetin microspheres	Quercetin	Significantly decreases the dose size	Anticancer	Solvent evaporation	6	In vitro
Cynara scolymus microspheres	Cynara scolymus extract	Controlled release of nutraceuticals	Nutritional supplement	Spray-drying technique	6-7	Oral

Table 3.3.6: Other novel vesicular herbal formulations³⁹

Formulations	Active ingredients	Applications	Biological activity	Droplet size	Route of administration
Capsaicin transferosomes	Capsaicin	Increase skin penetration	Analgesic	150.6 nm	Topical
Colchicine transferosomes	Colchicine	Increase skin penetration	Antigout	-	In vitro
Vincristine transferosomes	Vincristine	Increase entrapment efficiency	Anticancer	120 nm	In vitro
Matrine ethosome	Matrine	Improve the percutaneous permeation	Anti-inflammatory	110 ± 8 nm	Topical

Table 3.3.7: Some herbal drug nanoparticles³⁸

Formulations	Active ingredients	Biological activity	Method of preparation
Artemisinin nanocapsules	Artemisinin	Anticancer	Self assembly procedure.
CPT encapsulated nanoparticles	Camptothecin	Anticancer	Dialysis method.
Berberine-loaded nanoparticles	Berberine	Anticancer	Ionic gelation method.
Curcuminoids solid lipid nanoparticles	Curcuminoids	Anticancer and antioxidant	Micro-emulsion technique.

Table 3.3.8: Transferosomes³⁸

Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration
Capsaicin transferosomes	Capsaicin	Increase skin penetration	Analgesic	150.6 nm	Topical
Colchicine transferosomes	Colchicine	Increase skin penetration	Antigout	-	In-vitro
Vincristine transferosomes	Vincristine	Increase entrapment efficiency and skin penetration	Anticancer	120 nm	In-vitro

Table 3.3.9: Recent patents on herbal controlled release formulations³⁹

US patent No.	Active ingredients	Novel system incorporate
US 5948414	Opioid analgesic and aloe	Nasal spray
US 6340478 B1	Ginsenosides	Microencapsulated and controlled release formulations
US6890561 B1	Isoflavones	Microencapsulated formulation
US6896898 B1	Alkaloids of aconitum species	Transdermal delivery system
US patent 2005/0142232 A	Oleaginous oil of <i>Sesamum indicum</i> and alcoholic extract of <i>Centella asiatica</i>	Brain tonic
US patent 2007/0042062 A1	Glycine max containing 7s globulin protein extract, curcumin, <i>Zingiber officinalis</i>	Herbal tablet dosage form
US patent 2007/0077284A1	Opioid analgesic (phenanthrene gp)	Transdermal patch
US patent 7569236132	Flavonoids (such as quercetin) and terpenes (ginkgolide A, B, C and J)	Microgranules

3.4 applications of novel drug delivery system for herbal formulations

Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) for plant actives and extracts. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement 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 degradation⁴⁰.

4. CURRENT STATUS OF NDDS MARKET IN DIFFERENTNATION

4.1 herbal marketed preparations

4.1.1 ocusert

(Pilocarpol - Dr. Winzer Pharma, Ocusert - Allergan; ALZA; Janssen)

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 delivery⁴¹.

4.1.2 hair-growth herbal spray (Kunming Runyantang Cosmetics Co., Ltd.)

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 naphtha⁴².

Its functions are

1. Influence the keratoderma hydration.
2. Dissolve sebum within sebaceous gland duct.

4.1.3 herbal treatment for frozen shoulder (XIAFLEXin the U.S.)

Frozen shoulder, or adhesive capsulitis, afflicts people in three distinct stages, each lasting weeks or months. The first stage, "freezing," consists of the onset of pain and gradual loss of motion in the arm and shoulder. During the second period, the "frozen" stage, pain recedes but stiffness becomes pronounced. In the final weeks or months, "thawing" finally sets in. Herbal therapy can be effective part of managing the initial pain⁴³.

4.1.4 Herbal ointment (Harvest Healthceutical Pvt.Ltd.)

To combat the inflammation of the connective tissue surrounding your shoulder joints and muscles, make the massage cream developed by herbalist Jeanne Rose. In a double boiler, bring to a gentle bubble one quart olive oil, 8 ounces fresh cayenne or habenero chili peppers, 3 ounces fresh (or 4 ounces dried) rosemary and 2 ounces dried comfrey root that has been soaked in Boiling water for 20 minutes. Blend contents for 20 seconds, and heat and cool one more time. Strain the mixture; add 6 to 8 ounces beeswax or cocoa butter, and 20 drops each of the Following essential oils: lavender, marjoram, frankincense and eucalyptus. Pour into several small jars and allow solidifying before use⁴³.

4.1.5 Herbal treatments for acne (HERBALmax™, Admark Herbals Limited, India)

An acne breakout is annoying for some but for others, it's a source of deep embarrassment. The

shelves of cosmetic counters feature every new chemical, ointment and peel, promising to heal your pimples. If you're looking for something more natural and in tune with your body, try using herbal treatments in your quest for blemish-free skin⁴³.

4.1.6 Herbal treatment for colon cancer (National Library of Medicine U.S-BethesdaMD)

Colon cancer is the most common cancer of the digestive track. It mainly affects older people and there may be a genetic link. Since tumors can grow quite large without obstructing the bowel, the cancer can go undetected for quite a while and is not usually diagnosed until it has spread. There are many natural treatments that complement the standard course of treatment⁴³.

Causes

Colon cancer is closely linked with a high-fat and low-fiber diet. Animal fat restricts oxygen available to the good bacteria in a healthy colon. When deprived of oxygen, the bacteria produce Toxins. The lack of fiber slows down the rate at which toxins leave the body through the stool. Other possible causes are heredity, calcium deficiency, and chronic diarrhea and constipation.

Symptoms

The most notable symptom of colon cancer is blood in the stool. In addition, there may be a change in bowel habits, pain in the abdomen, acid stomach, and muscle tension and twitching in the stomach.

4.2 novel drug delivery systems market (NDDS) formulations (oral & injectable)

Novel drug delivery systems (NDDS) offer many advantages, which include improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration, and improved targeting for a specific site to reduce unwanted side effects. The challenge for both drug and drug delivery companies is to deliver both existing and emerging drug technologies in a manner that improves the current benefits enjoyed by the patients⁴³.

4.3 Marketed novel drug delivery formulations of plant active and extracts³⁹

Table 4.3: Marketed novel drug delivery formulations of plant active and extracts

S.No	Brand name	Plant active/extracts	Type of NDDS	Company name
1	White tea liposome Herbasec	Camellia sinensis extract	Liposome	Cosmetochem
2	Green tea liposome Herbasec	Camellia sinensis Extract	Liposome	Cosmetochem
3	White hibiscus liposome Herbasec	White hibiscus extract	Liposome	Cosmetochem
4	Aloe vera liposome Herbasec	Aloe vera Extract	Liposome	Cosmetochem
5	Guarana liposome Herbasec	Guarana extract	Liposome	Cosmetochem
6	Centella Phytosome	Triterpenes from Centella asiatica leaf	Phytosome	Indena
7	Crataegus Phytosome	Vitexin-2"-O-rhamnoside from Hawthorn flower	Phytosome	Indena
8	Escin β -sitosterol Phytosome	Escin β -sitosterol from horse chestnut fruit	Phytosome	Indena
9	GinkgoselectPhytosome	Ginkgoflavonglucosides, ginkgolides, bilobalide from Ginkgo biloba leaf	Phytosome	Indena
10	Ginselect Phytosome	Ginsenosides from Panax ginseng rhizome	Phytosome	Indena
11	Ginkgo biloba terpenes Phytosome	Ginkgolides and bilobalide from Ginkgo biloba leaf	Phytosome	Indena
12	Ginkgo bilobadimeric flavonoids Phytosome	Dimeric flavonoids from Ginkgo bilobaleaf	Phytosome	Indena
13	Greenselect Phytosome	Polyphenols from green tea leaf	Phytosome	Indena
14	Meriva	Curcuminoids from turmeric rhizome	Phytosome	Indena
15	PA ₂ Phytosome	Proanthocyanidin A ₂ from horse chestnut bark	Phytosome	Indena
16	Sericoside Phytosome	Sericoside from Terminalia sericea bark root	Phytosome	Indena
17	Siliphos	Silybin from milk thistle seed	Phytosome	Indena
18	Silymarin Phytosome	Silymarin from milk thistle seed	Phytosome	Indena
19	Virtiva	Ginkgoflavonglucosides, ginkgolides, bilobalide from Ginkgo biloba leaf	Phytosome	Indena
20	18 β -glycyrrhetic acid Phytosome	18 β -glycyrrhetic acid from licorice rhizome	Phytosome	Indena

4.4 Current status of novel drug delivery technology for phytotherapeutics

Herbal drugs constitute a major share of all the officially recognised systems of health in India viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy, except Allopathy. More than 70% of India's 1.1 billion populations still use these non-allopathic systems of medicine¹⁷. Currently, there is no separate category of herbal drugs or dietary supplements, as the Indian Drugs Act. However, there is a vast experiential-evidence base for many of the natural drugs²².

5. CONCLUSION

This review gives information about Novel drug delivery system in herbals, their types, formulation, herbal drugs used and current market status of Novel drug delivery system in herbals. This information useful in the form of base for the further research work, isolation of

chemical entities from Novel drug delivery system in herbals, formulation of Novel drug delivery system in herbals.

An extensive research is going on in the area of novel drug delivery and targeting for plant actives and extracts. However, research in this area is still at the exploratory stage. Many 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. Herbal 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. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthenes when administered through novel drug delivery system show much better absorption profile which enables them to cross the biological membrane, resulting enhanced bioavailability. Hence more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney, etc.) at similar or less dose as compared to the conventional plant extract or phytomolecule. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered using NDDS. Hence there is a great potential in the development of novel drug delivery systems for the plant actives and extracts. Today the stress is on patient compliance and to achieve this objective there is a spurt in the development of NDDS. As the herbal excipients are promising biodegradable materials, these can be chemically compatible with the excipients in drug delivery systems. In addition herbal excipients are non-toxic, freely available, and less expensive compared to their synthetic counterparts. They have a Major role to play in pharmaceutical industry. Therefore, in the years to come, there is going to be continued interest in the natural excipients to have better materials for drug delivery systems. Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. The drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. However, phytotherapeutics need a scientific approach to deliver the components in a novel manner to increase patient compliance and avoid repeated administration. This can be achieved by designing novel drug delivery systems for herbal constituents.

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