



RECENT DEVELOPMENT IN NOVEL HERBAL DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT

Herbal drugs are probably as old as human race. Preparations of plants or plant parts are widely used in medicine since ancient times. Till today, the use of phytomedicines is widespread in most of the world and other benefits meant for use to diagnose, treat, mitigate diseases of human beings or animals and to alter the structure or physiology of human beings or animals. Certain limitations of herbal medicines and phytochemicals such as instability in highly acidic pH, pre systemic metabolism in liver, solubility and absorption problems, can lead to drug levels below therapeutic concentration in the plasma, resulting in less or no therapeutic effects. Also, most of the plant actives such as glycosides, tannins, flavonoids, etc, are polar molecules and are poorly absorbed due to large molecular size - which limits the absorption via passive diffusion, and poor lipid solubility which severely limits their ability to cross the lipid-rich biological membranes. These limitations lead to reduced bioavailability and hence, low therapeutic index of plant actives. Incorporation of novel drug delivery technology to plant actives minimizes the presystemic metabolism, degradation of drug in the gastrointestinal tract, distribution / accumulation of drug in the non targeted tissues and organs, and hence, reduces the side effects and improves the therapeutic efficacy and ultimately, the patient compliance.

Keywords: *Herbal drugs, novel drug delivery system, niosomes, liposomes, dendrimers, phytosomes, etc.*

1. INTRODUCTION

Herbal drugs are probably as old as human race. Preparations of plants or plant parts are widely used in medicine since ancient times. Till today, the use of phytomedicines is widespread in most of the world and other benefits meant for use to diagnose, treat, mitigate diseases of human beings or animals and to alter the structure or physiology of human beings or animals.

Certain limitations of herbal medicines and phytochemicals such as instability in highly acidic pH, pre systemic metabolism in liver, solubility and absorption problems, can lead to drug levels below therapeutic concentration in the plasma, resulting in less or no therapeutic effects. Also, most of the plant actives such as glycosides, tannins, flavonoids, etc, are polar molecules and are poorly absorbed due to large molecular size - which limits the absorption via passive diffusion, and poor lipid solubility which severely limits their ability to cross the lipid-rich biological membranes. These limitations lead to reduced bioavailability and hence, low therapeutic index of plant actives. Incorporation of novel drug delivery technology to plant actives minimizes the presystemic metabolism, degradation of drug in the gastrointestinal tract, distribution / accumulation of drug in the non targeted tissues and organs, and hence, reduces the side effects and improves the therapeutic efficacy and ultimately, the patient compliance.

Herbal formulations are obtained from whole plant or from particular plant parts by treating extraction, distillation, expression, fractionation, purification, concentration, or fermentation. Herbal formulation includes tinctures, oils, powders, juices and process exudates.

There are many advantages of herbal drugs such as less side effects, more effectiveness, cost is low, easily available, more patient compliance and prominent therapeutic effects[1].

In novel drug delivery systems control of distribution of drug is achieved by incorporating the drug in carrier system or changing the structure of the drug at molecular level. It has some advantages such as increases the bioavailability, decreases the risk of toxicity, enhances stability. It gives protection from physical and chemical stability, sustained delivery, etc.

Drug delivery system used for administering the herbal medicine by traditional method is reduced the efficacy of the drugs. For long time herbal medicines were not considered for advancement as novel formulation due to absence of scientific knowledge and processing troubles such as standardization, extraction and identification of drug components in polyherbal system.

From few decades, considerable attention has been focused on the development of novel drug delivery system for herbal drugs. Herbal drugs become more popular in the 21st century for their application to cure variety of diseases with less toxic effects and better therapeutic effects. Novel herbal drug

carriers cure particular diseases by targeting exactly the affected zone inside a patient's body and transporting the drug to that affected area. Novel drug delivery system is advantageous in delivering the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with increase in bioavailability of drugs. In novel drug delivery technology, control of distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level(1-2).

Incorporation of herbal drugs in the delivery system also aids to increase solubility, enhanced stability, protection from toxicity, enhanced in pharmacological activity, improved tissue macrophage distribution, sustained delivery and protection from physical and chemical degradation[23].

Novel herbal drug carriers cure particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Novel drug delivery system is advantageous in delivering the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with increase in bioavailability of drugs. In novel drug delivery technology, control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. Incorporation of herbal drugs in the delivery system also aids to increase in solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, sustained delivery and protection from physical and chemical degradation. For example, liposomes act as potential vehicles to carry anti cancer agents by increasing amount of drug in tumour area and decrease the exposure or accumulation of drug in normal cells/tissues thereby preventing tissue toxicity effects. The phytosomal carriers have been studied for effective delivery of herbal extracts of ginseng (*Ginkgo biloba*) etc. Direct binding of phosphatidylcholine to herbal extract components led to better absorption characteristics as compared to conventional delivery of herbal extracts. Other vesicular assemblies like microspheres, nanoemulsions, polymeric nanoparticles etc. have been proved beneficial to carry herbal components. The present review article is aimed to provide an overview of different types of drug delivery systems incorporating active ingredients and potential advantages of such systems. In the present article, an attempt has been made to touch upon various aspects and applications related to novel herbal drug formulations

Types of Novel Herbal Drug Delivery System:

There are various types in case of novel herbal drug delivery system are given in figure below, which includes phytosomes, liposomes, niosomes, transferosomes, ethosomes and dendrimers, etc are discussed in given article.

1. Phytosome :

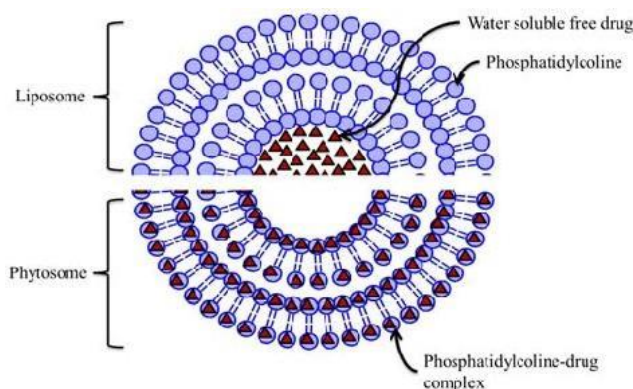


Figure no. 1 Phytosome

Phytosomes is vesicular drug delivery system in which photo constituents of herb extract surround and bound by lipid.

Water soluble phyto constituents molecules can be converted into lipid compatible molecular complexes, which are called phytosomes. Phytosomes having more bioavailability as compared to simple herbal extract owing to their enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood[4-6].

The lipid-phase substances employed to make phytoconstituents lipid compatible are phospholipids from soy, mainly phosphatidylcholine. Phytosomal complexes were first investigated for cosmetic applications, but mounting evidence of potential for drug delivery has been cumulated over the past few years, with beneficial activity in the realms of cardiovascular, anti-inflammatory, hepatoprotective and anticancer applications.

Advantages of phytosomes:

- Improve bioavailability in GIT.
- Higher stability

- Less dosing frequency
- Increased bioavailability due to phospholipid complex
- High penetrating capacity

Method of preparation of phytosome :

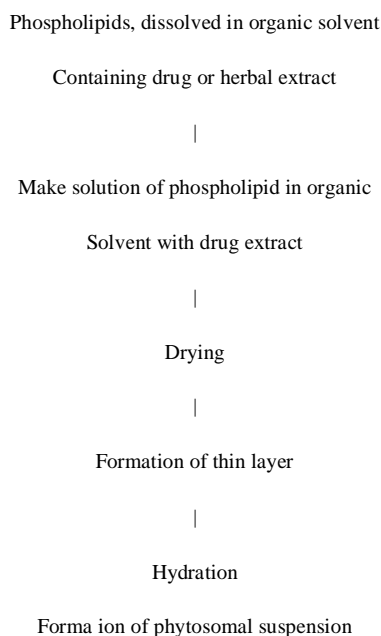


Figure No. 2 Stages for the preparation of phytosome

2. Liposome:

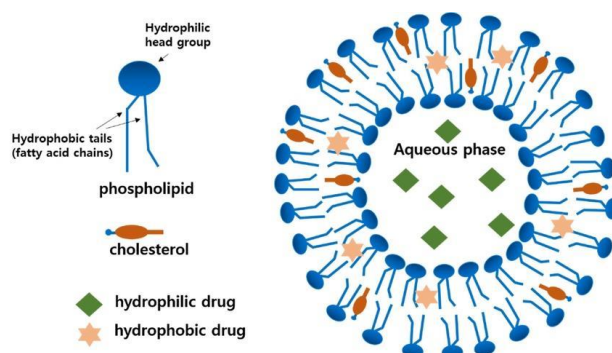


Figure no. 3 Liposome

Liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse or float into their interior. A liposome can be formed many sizes as uni- lamellar or multi-lamellar construction, and its name is related with their structures, phospholipid and do not related with their size. It does not necessarily contains lipophilic contents, like water. Liposomes are artificially prepared vesicles prepared vesicles made of lipid bilayer. It can be filled with drug or herbal drug and used to treat many more diseases such as cancer. Liposomes are micro particulate or colloidal carriers, usually 0.05-5.0 micrometer in diameter[8].

They can have one, several or multiple concentric membranes. 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. Liposomes are composed of relatively biocompatible and biodegradable material, and they consist of an aqueous volume entrapped by one or more

bilayer of natural and/or synthetic lipids Drug with widely varying lipophilicity can be encapsulated in liposomes, either in the phospholipids bilayer, in the entrapped aqueous volume or at the bilayer interface.

Advantages of liposomes:

- High biocompatibility.
- Easy to prepare.
- Increase efficacy and therapeutic index.
- Ability to carry both water and lipid soluble drugs.
- Reduction in toxicity.
- Increase stability.

2. CLASSIFICATION OF LIPOSOMES**On the basis of structural features:**

1. Multilamellar large vesicles
2. Unilamellar vesicles
 - i) Small unilamellar vesicles
 - ii) Sized unilamellar vesicles
 - iii) Large unilamellar vesicles
 - iv) Giant unilamellar vesicles

3. Oligolamellar vesicles

4. Multivesicular vesicles

On the basis of method of liposome preparation:

1. Single or oligolamellar vesicles made by reverse phase evaporation method.
2. Multilamellar vesicles made by reverse phase evaporation method
3. Stable plurilamellar vesicles
4. Frozen and thawed multilamellar vesicles
5. Vesicles prepared by fusion
6. Vesicles prepared by French press
7. Dehydration- rehydration vesicles

Method of preparation of liposome:

Method of preparation of liposomes involve four basic stages:

1. Drying down lipids from organic solvents.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analyzing the final product.

Method of liposome preparation and drug loading:

The following methods are used for the preparation of liposome:

1. Passive loading techniques
2. Active loading technique.

PASSIVE LOADING TECHNIQUES INCLUDE THREE DIFFERENT METHODS:

1. Mechanical dispersion method.

- Sonication.
- French pressure cell: extrusion.
- Freeze-thawed liposomes.
- Lipid film hydration by hand shaking, non-hand. shaking or freeze drying.
- Micro-emulsification.
- Membrane extrusion.

2. Solvent dispersion method.

3. Detergent removal method (removal of non-encapsulated material).

3. Niosome:

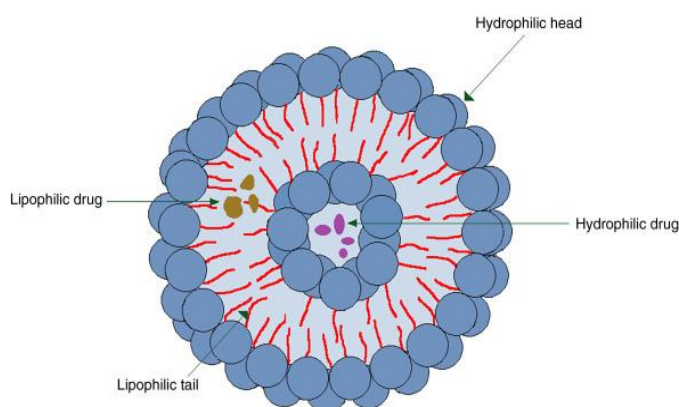


Figure no. 4 Niosome

Niosomes are microscopic multilamellar vesicles formed from mixture of non ionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media. Niosomes possess associate infrastructure consisting of both hydrophobic and hydrophilic moieties along and as a result will accommodate drug molecules with a solubility's. Niosomes are evaluated in several pharmaceutical applications. In such wide selection of therapeutic applications, important advantages of victimization niosomes embrace their ability to reduce toxicity by encapsulation of treatment agents and minimize clearance of such agents from the body by slow drug release.

Niosomes are different from liposomes in that they offer and advantages over liposomes, such as liposomes are expensive, their ingredients like phospholipids are chemically unstable, they require special storage and handling. Niosomes do not have any of these problems[2,25].

VARIOUS TYPES OF NIOSOME

Based on the vesicle size, niosomes can be divided into three groups. These are,

- Small unilamellar vesicles (SUV, size=0.025-0.05 μm),
- Multilamellar vesicles (MLV, size=>0.05 μm), and
- Large unilamellar vesicles (LUV, size=>0.10 μm).

3. METHODS OF PREPARATION

Niosomes are prepared by different methods based on the sizes of the vesicles and their distribution, number of double layers, entrapment efficiency of the aqueous phase and permeability of vesicle membrane[25].

PREPARATION OF SMALL UNILAMELLAR VESICLES:

1. Signification:

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial. The mixture is homogenised using a sonic probe at 60°C for 3 minutes. The vesicles are small and uniform in size.

2. Micro fluidisation:

Two fluidised streams move forward through precisely defined micro channel and interact at ultra-high velocities within the interaction chamber. Here, a common gateway is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility.

PREPARATION OF MULTILAMELLAR VESICLES:

1. Hand shaking method (Thin film hydration technique)

In the hand shaking method, surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform or methanol in a rotary evaporator, leaving a thin layer of solid mixture deposited on the wall of the flask. The dried layer is hydrated with aqueous phase containing drug at normal temperature with gentle agitation.

2. Trans-membrane pH gradient (inside acidic) drug uptake process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to obtain a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed three times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to produce the desired multilamellar vesicles.

PREPARATION OF LARGE UNILAMELLAR VESICLES

1. Reverse phase evaporation technique (REV)

In this method, cholesterol and surfactant are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline. The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with phosphate-buffered saline and heated in a water bath at 60°C for 10 min to yield niosomes.

Advantages of niosomes:

- Niosomes are biodegradable, biocompatible, non-toxic and non-immunogenic.
- Easy to store due to chemical stability.
- Administered by different routes.
- Better patient adherence.
- Niosomes are able to encapsulate large amount of materials in small volume of vesicles.
- Better effectiveness than conventional oily formulations.

4. Transfersome

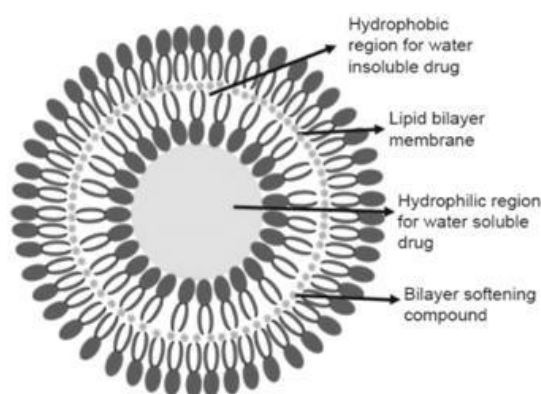


Figure no. 5 Transfersome

Transfersomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator this aqueous core surrounded by a lipid bilayer makes ultra-deformable vesicles having both self-optimizing and self-regulating capabilities. In accordance with that, transfersomes are elastic in nature and can thereby deform and squeeze themselves as intact wevesicles without a measurable loss through narrow pores or constrictions of the skin that are significantly smaller than the vesicle size. In contrast to conventional liposomes, which are comprised of natural (such as egg phosphatidylcholine-EPC and soybean phosphatidylcholine-SPC) or synthetic (such as dimyristoyl phosphatidylcholine DMPC, dipalmitoyl phosphatidylcholine-DPPC and dipalmitoyl phosphatidyl glycerol-DPPG) phospholipids, the modified liposomal vesicular system (transfersomes) is composed of the phospholipid component and single-chain surfactant as an edge activator. Edge activators (EAS) function in an exceptional manner as membrane-destabilizing factors to increase the deformability of vesicle membranes and, when combined in a proper ratio with an appropriate lipid, gives the optimal mixture, enabling the transfersomes to become deformable, as well as ultra-flexible, which results in a higher permeation capability[1 -3].

Transfersomes are specially optimized particles or vesicles, that can respond to an external stress by rapid and energetically inexpensive, shape transformations. The development of novel approaches like transfersomes have immensely contributed in overcoming problem faced by transdermal drug delivery such as unable to transport larger molecules, penetration through the stratum corneum is the rate limiting step, physicochemical properties of drugs hinder their own transport through skin. These elastic vesicles can squeeze themselves through skin pores many times smaller than their own size and can transport larger molecules.

Advantages of transfersomes:

- Transfersome have high entrapment efficiency.
- It have better penetration of Intact vesicles.
- It releasing their contents slowly and gradually.
- Used for both systemic as well as topical delivery of drug.
- Transfersomes are biocompatible and biodegradable.

5. Dendrimers:

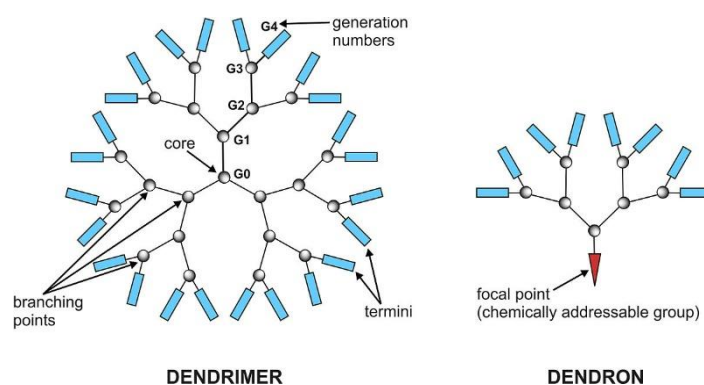


Figure no. 6 Dendrimers

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure consisting of tree-like arms or branches. Dendrimers are nearly monodisperse macromolecules that contain symmetric branching units built around a small molecule or a linear polymer core. 'Dendrimer' is only an architectural motif and not a compound. Polyionic dendrimers do not have a persistent shape and may undergo changes in size, shape, and flexibility as a function of increasing generations. Dendrimers are hyperbranched macromolecules with a carefully tailored architecture, the end groups (i.e., the groups reaching the outer periphery), which can be functionalized, thus modifying their physicochemical or biological properties [3]. Dendrimers have gained a broad range of applications in supramolecular chemistry, particularly in host-guest reactions and self-assembly processes. Dendrimers are characterized by special features that make them promising candidates for a lot of applications. Dendrimers are highly defined artificial macromolecules, which are characterized by a combination of a high number of functional groups and a compact molecular structure.

Advantages of dendrimers:

- Direct medication is possible to the affected part of the body.
- Controlled and sustained release.
- High drug loading is possible.
- Preservation of drug activity without any chemical reaction
- Increases therapeutic efficacy.
- Decreased side effects and renal clearance.

Methods of dendrimers drug delivery:

Currently, there are three methods used for drug delivery of dendrimers.

(a) The drug is attached to the periphery of the dendrimers to form dendrimer prodding.

(b) The drug is coordinated to the outer functional groups via ionic interaction.

(c) The dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer drug (i.e., host-guest) supramolecular assembly. The latter approach is of interest for multiple reasons and provides an opportunity to encapsulate pharmacologically active compounds and to study the supramolecular assemblies formed in these systems[9].

(d) Dendrimers possess several unique properties that make them a good nanoparticle platform for antimicrobial drug [23].

4. CONCLUSION

By incorporating the herbal drugs in NDDS, we can deliver the proper amount of dosage to the target site. Thus it concludes that, NDDS for herbal drugs will be a revolutionary application in the conventional herbal formulations which will save the time of preparations and will increase the patient compliance too.

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