Applications of Nanotechnology Based Dosage Forms for Delivery of Herbal Drugs.

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ABSTRACT

Over the past decade, major advances have been made on development of novel drug delivery systems (NDDS) form plant actives and extracts. Herbal medicines have been widely used all over the world since ancient old ages and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. Herbal therapeutics can be achieved by Drug Delivery systems. This herbal treatment helps to increase the therapeutic value by reduce the toxicity and side effects of drugs at the same time it also increase the bioavailability. The use of herbal formulations for novel drug delivery systems is more beneficial and has more advantages compared to others. The novel herbal formulations like liposomes, phytosomes, ethosomes microsphere, nanocapsules, transfersomes, polymeric nanoparticles, nanoemulsions and has been reported using bioactive and plant extracts. The main reason behind development of alternative drug delivery is to increase efficiency of drug delivery and safety in drug delivery and provide more convenience to the patient. Distribution, sustained delivery, and protection from physical and chemical degradation. The present work highlights the current status of the development of novel herbal formulations and summarizes their method of preparation, type of active ingredients, size, and entrapment efficiency, route of administration, biological activity and applications of novel formulations.

INTRODUCTION

During past decades, lot of attention has been paid on the improvement of novel drug delivery systems for herbal drugs. Novel herbal drug carriers help in cure of particular disease by targeting the affected area inside a patient's body and transporting the drug to that area. Novel drug delivery system is advantageous in delivering the herbal drug at optimum rate and delivery of drug at the site of action which minimizes the toxicity and enhances bioavailability of the 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 [1]. 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 [2]. However some limitations of herbal extracts/ plant actives like instability in highly acidic pH, liver metabolism etc. led to drug levels below therapeutic concentration in the blood resulting in less or no therapeutic effect [3]. Incorporation of novel drug delivery technology to herbal or plant actives minimizes the drug degradation or pre systemic metabolism, and serious side effects by accumulation of drugs to the non targeted areas and improves the ease of administration in the paediatric and geriatric patients. Various novel drug delivery systems such as liposomes, niosomes, microspheres and phytosomes have been reported for the delivery of herbal drugs. 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 [4]. The present article was aimed to provide insight of different types of drug delivery systems incorporating active ingredients and potential advantages of such systems.
Need For Novel Drug Delivery System for Herbal Drugs

Before reaching to the blood, many constituents of the herbal drugs will be smashed in the highly acidic pH of the stomach and other constituents might be metabolized by the liver. Resultant, the optimum quantity of the herbal drugs may not reach the blood. If the drug does not reach in the optimum amount to the infected region at “minimum effective level,” then there will be no means to show the therapeutic effect of the drug. Nanocarriers applying to herbal remedies will carry optimum amount of the drug to their site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism and increase the prolonged circulation of the drug into the blood due to their small size [5].

Advantages of Nanotechnology Based Dosage Forms

Nano-sized delivery system was selected because of the following reasons [5]:

- They appear to be able to deliver high concentrations of drugs to disease sites because of their unique size and high loading capacities.
- Deliver the drug in the small particle size that enhances the entire surface area of the drugs allocating quicker dissolution in the blood.
- The concentration seems to persist at the sites for the longer periods. Shows EPR (enhanced permeation and retention) effect, i.e., enhanced permeation through the barriers because of the small size and retention due to poor lymphatic drainage such in tumor.
- Exhibits passive targeting to the disease site of action without the addition of any particular ligand moiety.[5]
- Decrease in the side effects.
- Decrease in the dose of the drug formulation.

Types of Novel Herbal Drug Delivery Systems

Phytosome

Phytosomes are phospholipids-based drug delivery system has been found promising for 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 convensional delivery system and novel delivery system. The term Phytosome relates to “phyto”, which
means plant; while “some” means cell-like. 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.

Table 1: Herbal phytosome formulation

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

Advantages of phytosome formulation

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

- Liposome is used for drug delivery systems due to its unique structural properties.
- Liposome can carry both the hydrophobic and hydrophilic drug. Therefore, liposome as a drug carrier can indiscriminately deliver drugs through the cell membrane.
- Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene.
- Liposome formulation can produce sustained and controlled release of formulation and enhances the drug solubility.
Table 2: Herbal liposomal formulations

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

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 parti culates 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

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

Table 3: Herbal nanoparticulate formulations

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

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 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.

### Table 4: Herbal emulsion formulations

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

Advantages of emulsion-based formulations

- 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.
- As a result of the lipophilic drugs being made into o/w/o emulsion, the droplets of oil are phagocytosised by macrophages and increase its concentration in liver, spleen and kidney.
- 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, gelatine microspheres, polypropylene dextran microspheres, 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.

### Table 5: Microsphere herbal formulations

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

Advantage of microsphere formulation

- 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.
- Drug can be easily released from the formulation.
• 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/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. 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.

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Biological activity</th>
<th>Application of ethosomal formulations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sophora Alopecuroides</td>
<td>Anti-endotoxic, anti-cancer and anti-inflammatory</td>
<td>Ethosome enhances delivery of drugs through the stratum corneum barrier into the deep layer of the skin</td>
<td>[45]</td>
</tr>
<tr>
<td>Matrine</td>
<td>Antibacterial, anti-inflammation, anti-rheumatism and anti-tumour anti-inflammatory effect</td>
<td>Increase the per cutaneous permeation</td>
<td>[46]</td>
</tr>
</tbody>
</table>

Advantages of ethosomal drug delivery

• Ethosomes enhance transdermal permeation of drug through skin.
• Ethosomes are a platform for the delivery of large amounts of diverse groups of drugs.
• The ethosomal drug is administered in semisolid form, resulting in improved patient compliance.

**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. 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 bloodbrain 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. A variety of SLN herbal formulations are shown in Table 7.

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Biological activity</th>
<th>Applications of SLN herbal formulations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Anti-tumour, antioxidant and anti-inflammatory</td>
<td>activities Increase in stability</td>
<td>[49]</td>
</tr>
<tr>
<td>Curcuminoids</td>
<td>Anti-malarial activity</td>
<td>Increase in activity</td>
<td></td>
</tr>
</tbody>
</table>

Advantages of SLN herbal formulation

• It provides controlled release and site-specific drug targeting.
• Large-scale production can be done.
• In this formulation, both lipophilic and hydrophilic drugs can be loaded.
• Another advantage is that it is made of lipid matrix (physiological lipids), which decreases danger of chronic and acute toxicity.

**CONCLUSION**

Herbal medicine is globally accepted as an alternative system of therapy in the pharmaceuticals. But the drug delivery system for herbal drugs is quite traditional and out of date. 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. A number of plant constituents like flavonoids, tannins, terpenoids etc. showed enhanced therapeutic effect at similar or less dose when incorporated into novel drug delivery vesicles as compared to conventional plant extracts. Hence, there is a great potential in development of novel drug delivery system for valuable herbal drugs as it provides efficient and economical drug delivery. Also, the trend of incorporating NDDS for herbal drugs has also been adopted at industrial scale.

REFERENCES


