HERBAL DRUG DELIVERY SYSTEMS: AN EMERGING AREA IN HERBAL DRUG RESEARCH

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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’s population. In the modern world, herbal drugs are popular due to their ability to cure a variety of diseases with less toxic and better therapeutic effects.

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 metabolism, 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.

Novel drug delivery systems (NDDS) for herbal drugs

The novel drug delivery system used with herbal drugs should be able to channelize the active entity of herbal drug to its site of action at a rate directed by the needs of the body / chronopharmacology of the disease, throughout the period of treatment. Various NDDS that have been used with herbal drugs and phytochemicals may be broadly classified into the following groups:

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

Abstract

Plant based drugs are used by the human race since times immemorial for different ailments. But, these phytomedicines suffer limitations, which are mainly due to stability issues and poor lipid solubility. To overcome these problems, novel drug delivery systems are being developed for phytomedicines. These herbal novel drug delivery systems include vesicular delivery systems such as liposomes, phytosomes, ethosomes, transfersomes, particulate delivery systems such as microspheres, micropellets, nanoparticles, and micro and nano emulsions. Many herbal drugs have been incorporated into these systems for improvement of stability, bioavailability and reduction of toxicity. The present review highlights the current status of the development of novel herbal formulations and their applications in therapy.

Key Words: Liposome, Phytosome, Ethosome, microemulsion, Micropellets, Nanoparticle
2. **Particulate delivery systems**, which include microspheres, nanoparticles, micropellets
3. **Biphasic systems**, such as micro/nano emulsions

**Vesicular delivery systems**

**Liposomes**

Liposomes are biodegradable, colloidal and spherical vesicles of 0.05-5.0 μm diameter, composed of a lipid bilayer membrane entrapping an aqueous core. They are specifically advantageous in enhancing the therapeutic index of anti-cancer agents, by increasing the drug concentration in the tumour cells and decreasing the exposure to normal cells. Essential oil from rhizomes of *Atractylodes macrocephala* Koidz has been entrapped into liposomes – which is useful for the treatment of digestive diseases and tumors – with reduced side effects. Extracts of *Tripterygium wilfordi* have been incorporated into liposomes to increase the temperature stability and also to reduce the side effects. Quercetin liposomes have been prepared for oral and intranasal delivery with increased anxiolytic and cognitive effects with decreased dose. The herbal drugs incorporated into liposomes along with the purpose of incorporation are given in Table 1.

**Phytosomes**

Hydrophilic phytoconstituents can be complexed with clinically useful nutrients such as phospholipids to convert them into lipid soluble complexes. Such complexes can be used to prepare liposome-like vesicles called as phytosomes. In phytosomes, the complexation of phospholipids and water soluble active plant components involve chemical bond formation and therefore more stable. Whereas in liposomes no chemical bond is formed; phosphatidylcholine molecules simply surround the water-soluble components (Fig. 1). The phytosomes substantially improve the bioavailability of these hydrophilic active components. Some of the phospholipids that are reported for phytosome preparation include soy phospholipids, phosphatidylethanolamine etc. Phytosomes can easily cross the lipid membranes and are reported to increase the bioavailability of poorly lipid soluble plant based drugs by increasing the absorption in gastrointestinal tract. Some of the phytoconstituents incorporated in phytosomes include extracts of *Ginkgo biloba*, grape seed, hawthorn, milk thistle, green tea and ginseng.

Phytosomes containing different herbal drugs are commercialized in USA. Some of the commercial phytosomes are given in Table 2.

**Transferosomes**

Transferosomes are phospholipid vesicles particularly used as carriers for the transdermal delivery of the drug. They are reported to overcome the problem of penetration through the stratum corneum due to hydration or osmotic force in the skin. The formulation of transferosomes includes phospholipids which act as vesicle forming material, surfactants to provide flexibility, alcohol as solvent and buffering agent as Hydrating medium.

Xiao-Ying et al (2006) have reported capsaicin transferosomes prepared by the high shear dispersion technique. It is reported that the transdermal penetration of the capsaicin was higher in transferosomes, resulting in better topical absorption as compared to pure drug. The bioavailability of curcumin has been increased by incorporating it in transferosome-containing topical gel, which has been reported to increase the penetration through skin. The transferosomal preparation of colchicine, an anti-gout agent, is reported to prevent the gastrointestinal side effects associated with oral administration of colchicine. Vincristine sulfate transferosomes prepared with lecithin and sodium deoxycholate have been reported to maintain zero order kinetics of the drug diffusion through the skin.

**Ethosomes**

Ethosomes are vesicles composed of phospholipids and high concentration of ethanol. The high concentration of ethanol in the ethosomes enhances their permeability through the skin by fluidising the skin lipids. These carriers can penetrate through the skin deeply leading to improved drug delivery into deeper layers of skin and even into blood circulation. Ethosomes of Triptolide were prepared for topical delivery of the drug. The ethosomal formulation showed an increase in bioavailability in rats due to increase in the accumulation and reduction in erthema more rapidly as compared to the other formulations. Ethosomal preparations of ammonium glycyrrhizinate – for the treatment of inflammatory diseases of skin – exhibited improved bioavailability as compared to ethanolic solution of drug. The ethosomes did not exhibit any toxicity. Ethosomes of alkaloids of *Sophora alopecerides* enhanced the permeability of the drug through the stratum corneum.
Table 1. Herbal liposomal drug delivery systems7-12

<table>
<thead>
<tr>
<th>Herbal drug</th>
<th>Purpose</th>
<th>Medicinal Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential oil from Atractylodes macrocephala Koidz</td>
<td>Increase in solubility and bioavailability</td>
<td>Anti-arthritis</td>
</tr>
<tr>
<td>Extracts of <em>Tripterygium wilfordii</em> (Triptolide)</td>
<td>Increase stability</td>
<td>Angiogenesis inhibitor, anticancer, polycystic kidney disease, digestive disorders</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Increase in bioavailability and reduction in side effects</td>
<td>Anticancer / Antioxidant</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Increase in hepatoprotective activity</td>
<td>Hepatoprotective</td>
</tr>
<tr>
<td>capsacin</td>
<td>Increase in permeation and prolongation of action</td>
<td>Neuropathy, Neuralgia, arthritis</td>
</tr>
<tr>
<td>Artemisia arborescens L. essential oil</td>
<td>Increase in the stability and antitherpetic property</td>
<td>Anti-herpes</td>
</tr>
</tbody>
</table>

Table 2. Commercial phytosome preparations13-16

<table>
<thead>
<tr>
<th>Herbal Source</th>
<th>Phytoconstituent</th>
<th>Medicinal Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silybium marianum</td>
<td>Sylbibin flavonoids</td>
<td>Hepatoprotective, antioxidant</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Ginkgo flavonoids</td>
<td>Protects brain and vascular linings</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Ginsenosides</td>
<td>Nutraceutical, immunomodulator</td>
</tr>
<tr>
<td>Thea sinensis</td>
<td>Epicallocatechin</td>
<td>Systemic antioxidant and anticancer</td>
</tr>
<tr>
<td>Olea europaea oil</td>
<td>Polyphenols</td>
<td>Antioxidant, anti-inflammatory and anti hyperlipidemic</td>
</tr>
</tbody>
</table>

Fig. 1. Difference between phytosomes and liposomes13
**Particulate delivery systems**

**Microspheres**
Microspheres are spherical particles of 1-1000 µm size, in which the drug is uniformly dispersed in polymer matrix and gets released following first order kinetics.25 Various natural and synthetic polymers used for microsphere preparation include albumin, gelatine, modified starches, polypropylene, dextran, polyactic acid and poly lactide-co-glycolide etc.25 The microspheres and micropellets have large surface-to-volume ratio. The interfacial properties of microspheres often dictate their activity.25 These can be administered by either oral route or by injection. Emulsion – solvent evaporation, spray drying and chemical cross-linking are the major techniques used for preparation of microspheres. Gastroretentive floating microspheres of silymarin have been reported for sustained delivery of the drug. A prolonged release of drug for a period of 12 h was achieved, which resulted in increased bioavailability of the drug.26 Microencapsulation of Zedoary turmeric oil into microspheres has been used for bioavailability enhancement and sustaining the release.27 The reported microspheres of different herbal drugs are given in Table 3.

**Nanoparticles**
Nanoparticles are the submicron size particles diameter of around 200 nm made up of biodegradable and non-biodegradable polymers. The advantages of the nanoparticles include enhanced stability, long term storage, increased solubility of components, improved absorption of incorporated drug and reduction in the dose and dose related side effects. Nanoparticles can be used for controlled release as well as for targeting the drug to particular tissue or organ.31 Nanoparticle systems have been reported in literature, for curcuminoids, paclitaxel, and praziquantel.32-34 Reported nanoparticles of different herbal drugs and phytoconstituents are given in Table 4.

Curcumin from the rhizomes of *Curcuma longa* has the anticancer activity. But due to its poor aqueous solubility and poor bioavailability, the activity is limited. The nanoparticles of curcumin using cross-linked random copolymers of Nisopropylacrylamide with N-vinyl-2-pyrrolidone and polyethylene glycol monoacrylate resulted in improved bioavailability.35 Nanocapsules of Zedoary turmeric oil have exhibited increased hepatoprotective and anticancer effects of the incorporated oil.36 Nanoparticles of paclitaxel have been reported for controlled delivery of the drug with reduced toxic effects.38

**Micropellets**
These are the solid particles with size range of 1-1000 µm. In micropellets, the drug could be either dissolved or dispersed in the polymeric solutions and spray-dried. Spray drying provides a single step, rapid drying process, which can be scaled up and be used for heat-sensitive drugs. Controlled release pellets are used for the delivery of drugs to specific sites and for the extended period of time. The pellets prevent dose dumping, which is common with conventional dosage forms.40 Alginate-based micropellets of andrographolide from *Andrographis paniculata* have been reported to release the drug away from the upper GIT and hence prevent the GIT irritation and its associated problems such as loss of appetite, nausea and vomiting.41 Pectin- HPMC coated curcumin pellets are reported for delivery of curcumin to colon for the treatment of inflammatory disease.42 The extract of *Piper sarmentosum* was entrapped into calcium alginate microbeads. It was found that the encapsulation efficiency of drug is independent of the encapsulation method.29

**Micro/ Nano Emulsions**
Micro and nanoemulsions are the o/w type emulsions with size range varying from several nanometers to few microns. They can be prepared by the high pressure homogenization and microfluidization techniques.43,44 Many herbal drugs and phytoconstituents have been incorporated into micro emulsions for different purposes. Such delivery systems are given in Table 5. Self-microemulsifying drug delivery system has been reported for curcumin to increase its oral absorption. The microemulsion was formulated using surfactant, cosurfactant and ethyl oleate. An increase in the oral absorption of curcumin was observed with the self microemulsifying drug delivery system as compared to the simple emulsion.45 Self nanoemulsified drug delivery system was developed for the delivery of the ubiquinone. This system increased the solubility of the drug, thereby enhancing the bioavailability. Also, this system was found to decrease the precipitation of drug in the vehicle.46

Apart from the above discussed delivery systems, there are many more drug delivery systems for the herbal constituents, which include polymeric micelles, implants and polymer-phytochemical complexes. But, these are still in developmental stage and much work is further needed in these areas of research.
Table 3. Herbal microspheres and their applications

<table>
<thead>
<tr>
<th>Herbal drug</th>
<th>Purpose</th>
<th>Medicinal Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutin</td>
<td>Site-specific delivery to cardiovascular and cerebrovascular region</td>
<td>Cardiovascular and cerebrovascular agent</td>
</tr>
<tr>
<td>Camptothecin</td>
<td>Dose reduction, enhancement of cytotoxicity</td>
<td>Cytotoxic, anticancer</td>
</tr>
<tr>
<td>Sylimarin</td>
<td>Sustained release, enhancement of activity</td>
<td>Hepatoprotective activity</td>
</tr>
<tr>
<td>Turmeric oil</td>
<td>Sustained release, increase in bioavailability</td>
<td>Hepatoprotective, anticancer, antibacterial</td>
</tr>
</tbody>
</table>

Table 4. Herbal nanoparticles

<table>
<thead>
<tr>
<th>Herbal drug</th>
<th>Purpose</th>
<th>Medicinal Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Solubility and bioavailability enhancement</td>
<td>Anticancer activity</td>
</tr>
<tr>
<td>Zedoary turmeric oil</td>
<td>Enhancement of stability, hepatoprotective activity and anticancer effects</td>
<td>Anticancer, hepatoprotective</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Enhancement of antioxidant activity</td>
<td>Antioxidant and anticancer</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Reduction of side effects</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Paclitaxel and Doxorubicin</td>
<td>Reduction of side effects / Avoidance of resistance</td>
<td>Anticancer</td>
</tr>
</tbody>
</table>

Table 5. Herbal micro/ nano emulsions

<table>
<thead>
<tr>
<th>Herbal Drug</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Enhancement in oral bioavailability</td>
</tr>
<tr>
<td>Ubiquinone self-nano-emulsified delivery</td>
<td>Enhancement in solubility, bioavailability and avoidance of precipitation of drug in the vehicle</td>
</tr>
<tr>
<td>Zedoary turmeric oil</td>
<td>Improvement in aqueous dispersibility, stability and oral bioavailability</td>
</tr>
<tr>
<td>Docetaxel submicron emulsion</td>
<td>Improvement of residence time for better anticancer activity</td>
</tr>
<tr>
<td>Berberine nanoemulsion</td>
<td>Improvement of residence time, absorption and enhancement of anticancer activity</td>
</tr>
<tr>
<td>Quercetin microemulsion</td>
<td>Enhancement of penetration into stratum corneum and epidermis; Better antioxidant activity</td>
</tr>
</tbody>
</table>

**Conclusion**

Application of novel drug delivery systems to phytoconstituents can lead to enhanced bioavailability, increased solubility and permeability, thereby reducing the dose and hence, side effects. A number of plant constituents have exhibited enhanced therapeutic effect at similar or less dose when incorporated into novel drug delivery systems as compared to conventional extracts. Hence, there is great potential in development of novel drug delivery system for valuable herbal drugs.

**Declaration of Interest**

It is hereby declared that this paper does not have any conflict of interest.
References


