Herbal Medicine Incorporated Nanoparticles: Advancements in Herbal Treatment

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Abstract
Use of herbal medicines dates back a long history. These days the use of herbal medicines has increased because of their ability to treat different diseases with fewer side effects. However, the effective drug delivery of herbal medicines has not still been achieved. Different scientific approaches are being developed these days to deliver herbal medicines. Novel formulations including nanoparticles have been developed for the effective delivery of herbal drugs. Nanoparticulate formulations such as polymeric nanoparticles, liposomes, proliposomes, solid lipid nanoparticles and microemulsions present potential to deliver herbal medicines effectively. This article summarizes various nanoparticulate technologies that have been studied for the delivery of herbal medicines and which are gaining more attention for improved therapeutic response.

Key words: Herbal medicine, novel formulation, nanoparticle, drug delivery, drug targeting

Cite this article as:
1. Introduction
Herbal remedies have been in practice since thousands of years and are a part of culture in countries like China, India and even Nepal. In recent decades the use of herbal drugs has significantly increased which is evident from the increased global market of herbal medicines. Since herbal medicines have fewer side effects as compared to synthetic ones, their use has been increasing. Additionally, development of herbal dietary supplements and nutraceuticals have led to an increase in herbal market share. However, the use of novel drug delivery systems for the formulation of herbal medicines is slow when compared to the complexity of the active constituents. Although several formulations for herbal drugs have been developed and they have demonstrated efficacy similar to that of chemically synthesized modern drugs, a lot more investigation is still warranted.

Among the novel drug delivery systems, nanoparticles are considered to be an important one. Nanoparticle can be used to target the herbal medicine to individual organ which improves the selectivity, drug delivery, effectiveness and safety and thereby reduces dose and increases patient compliance. The requirement of an ideal nanoparticle system is that it should be capable of circulating in blood stream and should be small enough to reach target cells and tissues. Herbal medicines can be targeted to various organs such as brain, lung, liver, kidney, gastrointestinal tract, etc. The overall activity of herbal medicines depend on the active constituents present in them since they provide synergistic action and thus enhance the therapeutic value. Most of the herbal actives are poorly water soluble because of their hydrophobic nature. This property leads to decreased bioavailability and increased systemic clearance thus necessitating repeated administration or increased dose, and thus limits the clinical use of herbal medicines. Therefore, nanoparticles can be utilized to increase the herbal drug solubility and help to localize the drug in a specific site thus resulting in better efficacy and improved patient compliance.

Development of different herbal medicine incorporated nanoparticle formulations
Different nanoparticle formulations have been developed to deliver herbal formulations. They are described below:

Polymeric nanoparticles:
Nanoparticles refer to colloidal systems with particle size ranging from 10 to 1000 nm. Nanoparticles have several advantages including solubility enhancement, bioavailability enhancement, efficacy enhancement, dose reduction and improved absorption of herbal medicines compared to traditional herbal dosage forms. Liu et al. developed triptolide-loaded poly (DL-lactic acid) nanoparticles. To overcome the problems of poor solubility and toxicity of triptolide, nanoparticles were developed with biocompatible and biodegradable polymers, poly (DL-lactic acid). They were uniform in size, spherical in shape with smooth surface. Sahu et al. synthesized a new biodegradable and self-assembling polymer, methoxy poly (ethylene glycol)-palmitate, for curcumin delivery to cancer cells. The system comprised of methoxy poly (ethylene glycol) as hydrophilic part, palmitic acid as hydrophobic part and curcumin was present in the core of polymer micelle. The prepared micellar nanocarriers were spherical in shape.

For the prevention of the hydrolysis of camptothecin in physiological condition, Min et al. developed hydrophobically modified glycol chitosan nanoparticles-encapsulated camptothecin for tumor targeting and better stability. The hydrophobic 5β-cholanic acid moiety was chemically conjugated with hydrophilic glycol chitosan backbone and camptothecin was encapsulated for intravenous administration.

Hypericin is a highly lipophilic agent and hence insoluble in physiologically acceptable media which makes its systemic administration problematic and restricts its diagnostic applications. To overcome these problems, an injectable suspension of polymeric nanoparticles with hypericin was developed using biodegradable and biocompatible synthetic polymers such as poly lactic acid (PLA) or polylactic-co-glycolic acid (PLGA) for better photodetection and photodynamic therapy for the early diagnosis of cancer.

Yang et al. developed nanoparticles of Cuscuta chinensis by nanosuspension method to improve absorption of poorly water soluble constituent, quercetin. Similarly, Zhang and Kosaraju studied a biopolymeric delivery system for controlled release of catechin. The antioxidant activity of catechin is decreased dramatically when it is introduced in an alkaline environment. In order to protect catechin, chitosan encapsulated catechin particles were developed. Also, Bhata et al. developed chitosan nanoparticles for the extract of Ziziphus mauritiana and checked the effect on its immunomodulatory activity.

Further information about the use of polymeric nanoparticles in herbal medicine delivery is presented in Table 1.
<table>
<thead>
<tr>
<th>Herbal medicine</th>
<th>Chemical classification</th>
<th>Pharmacological activity</th>
<th>Polymeric nanoparticle formulation</th>
<th>Particle size</th>
<th>Encapsulation efficiency</th>
<th>Benefit of formulation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptolide</td>
<td>Diterpenoid trioxepoxide obtained from traditional Chinese medicine <em>Tripterygium wilfordii Hook F</em></td>
<td>Used in the treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia and antineoplastic activity in vitro and in vivo</td>
<td>Poly (DL-lactic acid) nanoparticles</td>
<td>149.7 nm</td>
<td>85.7%</td>
<td>Enhanced solubility of triptolide and reduced toxicity</td>
<td>11</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Natural polyphenol isolated from the root of <em>Curcuma longa</em></td>
<td>Antitumor, antioxidant, antiplatelet aggregation and antimicrobial activity</td>
<td>Methoxy poly(ethylene glycol)-palmityl nanocarrier</td>
<td>41.43 nm</td>
<td>100%</td>
<td>Enhanced solubility and bioavailability of curcumin</td>
<td>12</td>
</tr>
<tr>
<td>Camptothecin</td>
<td>Cytotoxic quinoline alkaloid isolated from bark and stem of the oriental tree <em>Camptotheca acuminata</em></td>
<td>Used in the treatment of gastric, rectum, bladder, colon, lung, breast and ovarian cancers</td>
<td>Glycol chitosan nanoparticles</td>
<td>280-330 nm</td>
<td>80%</td>
<td>Improved solubility and stability of camptothecin with sustained release</td>
<td>13</td>
</tr>
<tr>
<td>Hypericin</td>
<td>Anthracene glycoside occurring in <em>Hypericum perforatum</em></td>
<td>Photosensitizer used in photochemotherapy</td>
<td>Polylactic acid/polyactic-co-glycolic acid nanoparticles</td>
<td>200-300 nm</td>
<td>70%</td>
<td>Increased hypericin solubility</td>
<td>14</td>
</tr>
<tr>
<td>Cuscuta chinensis (Active constituents - flavonoids and lignans such as quercetin, kaempferol)</td>
<td>Obtained from Chinese herbal medicine <em>Cuscuta chinensis Lam</em></td>
<td>As tonic for the liver and kidney. Used to improve sexual function, prevent senescence and regulate the immune system. Some studies showed antitumor, antiangiogenic, anti-inflammatory and immune-stimulatory effects</td>
<td>Nanoparticles (nanosuspension)</td>
<td>267 nm</td>
<td>90%</td>
<td>Enhanced solubility</td>
<td>15</td>
</tr>
<tr>
<td>Catechins (Active constituents - (+)-catechin, (-)-epicatechin, (-)-epigallocatechin-3-gallate)</td>
<td>Polyphenolic plant metabolites abundant in teas derived from the tea plant <em>Camellia sinensis</em></td>
<td>Chemopreventive, anticarcinogenic, antiviral, antioxidant, anti-obesity, anti-inflammatory, anti-diabetic, anti-mutagenic, anti-angiogenic, antibacterial, anti-aging activities</td>
<td>Chitosan nanoparticles</td>
<td>1.97-6.83 µm</td>
<td>27.9-40.12%</td>
<td>Increased stability of catechins</td>
<td>16</td>
</tr>
<tr>
<td>Plant extract of <em>Ziziphus mauritiana</em></td>
<td>Plant extract of <em>Ziziphus mauritiana</em></td>
<td>Immunomodulatory activity</td>
<td>Chitosan nanoparticles</td>
<td>-</td>
<td>-</td>
<td>Enhanced immunomodulatory activity of extract</td>
<td>17</td>
</tr>
</tbody>
</table>

### Table 1: Polymeric nanoparticle herbal formulations

**Liposomes**

Liposomes are nanoparticulate systems that have been developed since more than four decades for drug delivery to specific site in the body. Some properties like amphiphilicity, biocompatibility and biodegradability of liposomes are important for delivery of herbal drugs. Further advantages include improvement of therapeutic efficacy and safety, increased bioavailability, sustained release and localized drug delivery. Sou et al. developed a modified nano-lipid vehicle loaded with curcumin to deliver it into tissue macrophages through intravenous injection. Curcumin was encapsulated into a phospholipid vehicle comprising 1,2-dimyrystoyl-sn-glycero-3-phosphocholine; 1,5-dihexadecyl ester; 1,2-distearoyl-...
sn-glycero-3-phosphoethanolamine-N-[monomethoxy poly(ethylene glycol) (5000)] in a molar ratio of 10:1:0.06. Fang et al.31 studied liposomal formulation encapsulating tea catechins. Permeation studies showed appreciable permeation of (+)-catechin when encapsulated in liposomes formulated with anionic surfactant deoxycholic acid and dicetyl phosphate in the presence of 15% ethanol. Another study by Lee et al.32 developed calcium pectinate gel beads entrapping catechin-loaded liposomes for oral sustained delivery. Also, Samaligy et al.28 increased the bioavailability of silymarin using buccal liposomal delivery systems. The liposomal formulations are further presented in Table 2.

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<tr>
<td>Curcumin</td>
<td>Natural polyphenol isolated from the root of Curcuma longa</td>
<td>Antitumor, antioxidant, anti-inflammatory</td>
<td>-</td>
<td>Improved intravenous delivery of curcumin to tissue macrophages</td>
<td>30</td>
</tr>
<tr>
<td>Catechins (Active constituents - (+)-catechin, (-)-epicatechin, (-)-epigallocatechin-3-gallate)</td>
<td>Polypehonic plant metabolites abundant in teas derived from the tea plant Camellia sinensis</td>
<td>Chemopreventive, anticarcinogenic, antiviral, antioxidative, anti-obesity, anti-inflammatory, anti-diabetic, antimutagenic, antiangiogenic, antibacterial, antiaging activities</td>
<td>-</td>
<td>Improved loading and in vivo deposition of catechins</td>
<td>31</td>
</tr>
<tr>
<td>Silymarin (Active constituents - silybin, taxifolin, isoisilybin, silydianin, silychristin)</td>
<td>Flavonol glycoside obtained from dried fruits of Silybus marianum</td>
<td>Hepatoprotective agent</td>
<td>70%</td>
<td>Improved permeation and stability of silymarin</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 2: Liposome herbal formulations

**Proliposomes**
Although liposomes possess several advantages for drug delivery, they still have some disadvantages of physicochemical instability (aggregation, sedimentation, fusion, phospholipid hydrolysis, oxidation and sterilization in large scale production). In order to overcome these problems a novel method for liposome production has been reported, namely proliposomes.33-34 Proliposomes are dry, free flowing particles that immediately form liposomal suspension in contact with water. Solid properties of liposomes help resolve the stability problems of liposomes. Yan-yu et al.35 conducted a study on oral bioavailability of silymarin encapsulated into proliposome. Silymarin proliposomes had > 90% encapsulation efficiency with particle size of 196.4 nm. The study indicated improved bioavailability of silymarin in proliposome form as compared with pure silymarin.

**Solid lipid nanoparticles**
Solid lipid nanoparticles are nanoparticles ranging from 50-1000nm that are made from lipids which remain in a solid state at room and body temperature. Lipids used include mono-, di-, or triglycerides, lipid acids, and glyceride mixtures or waxes that are stabilized by the biocompatible surfactants. There are several advantages of solid lipid nanoparticles which include controlled drug release and drug targeting, protection of drug from chemical degradation, reduction of drug toxicity, enhancement of bioavailability, biodegradation, good tolerability, ability to incorporate both hydrophilic and lipophilic drugs, no problem with respect to large scale production and sterilization. The formulations incorporating herbal drugs in solid lipid nanoparticles include mouthwashes (e.g. peppermint oil), gargles (e.g. thymol) and inhalations (e.g. eucalyptus oil).36-38 Mei et al.39 prepared triptolide incorporated solid lipid nanoparticles and studied the anti-inflammatory activity and transdermal delivery capacity. The formulation consisted of 5% tristearin glyceride, 1.2% soybean lecithin and 3.6% polyethylene glycol (400) monostearate. In other study, Mei et al. tried to reduce the hepatotoxicity induced by triptolide and improved its anti-inflammatory activity by formulating triptolide-incorporated solid lipid nanoparticles.40
Chen et al.\textsuperscript{41} prepared podophyllotoxin-loaded solid lipid nanoparticles and used them to target epidermis for the treatment of genital warts. Tiyaboonchai et al.\textsuperscript{37} studied the stability of curcuminoid (curcumin, demethoxycurcumin and bisdemethoxycurcumin)-loaded solid lipid nanoparticles in cream because curcuminoids degrade by acidic and alkaline hydrolysis, oxidation and photodegradation. In another study, Li et al.\textsuperscript{38} developed traditional Chinese medicine tetrandrine incorporated solid lipid nanoparticles to enhance the solubility of lipophilic tetrandrine. Hu et al.\textsuperscript{39} prepared cryptotanshinone incorporated solid lipid nanoparticles to enhance the bioavailability of cryptotanshinone. Another study by Shi et al.\textsuperscript{43} prepared solid lipid nanoparticles loaded with frankincense and myrrh oil. Further explanation of the solid lipid nanoparticle formulations is presented in Table 3.

<table>
<thead>
<tr>
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<td>Triptolide</td>
<td>Diterpenoid triepoxide obtained from traditional Chinese medicine Tripterygium wilfordii Hook F</td>
<td>Used in the treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia and antineoplastic activity\textsuperscript{18-20}</td>
<td>&lt;200 nm</td>
<td>-</td>
<td>Enhanced anti-inflammatory and transdermal delivery of triptolide</td>
<td>39</td>
</tr>
<tr>
<td>Podophyllotoxin</td>
<td>Podophyllotoxin is a compound of resin mixture known as podophyllin obtained from the dried roots of Podophyllum peltatum</td>
<td>Antivirus in the treatment of warts through topical application and anticancer activity\textsuperscript{41}</td>
<td>73.4 nm</td>
<td>-</td>
<td>Reduced hepatotoxicity of triptolide</td>
<td>40</td>
</tr>
<tr>
<td>Curcuminoids</td>
<td>Natural polyphenol isolated from the root of Curcuma longa</td>
<td>Antitumor, antioxidant, antiamyloidin, antiplatelet aggregation and anti-inflammatory\textsuperscript{21}</td>
<td>447 nm</td>
<td>70%</td>
<td>Enhanced stability of curcuminoids</td>
<td>37</td>
</tr>
<tr>
<td>Tetrandrine</td>
<td>Bisbenzylisoquinoline alkaloid extracted from the roots of Stephania tetrandria</td>
<td>Anti-inflammatory, antiplatelet aggregation, and free radical scavenging activity\textsuperscript{21}</td>
<td>157.3 nm</td>
<td>90.59%</td>
<td>Enhanced solubility and encapsulation of tetrandrine</td>
<td>38</td>
</tr>
<tr>
<td>Cryptotanshinone</td>
<td>Cryptotanshinone is the major active ingredient from the roots of Salvia miltiorrhiza Bunge</td>
<td>Anti-inflammatory, cytotoxic, antibacterial, anti-parasitic, anti-angiogenic and anti-oxidative\textsuperscript{44-48}</td>
<td>121.4-137.5 nmm</td>
<td>94.2-96.3%</td>
<td>Enhancement of bioavailability of cryptotanshinone</td>
<td>42</td>
</tr>
</tbody>
</table>

**Table 3: Solid lipid nanoparticle herbal formulations**

**Microemulsion**

Microemulsion is a system of oil, water and amphipile that is optically isotropic and thermodynamically stable liquid solution.\textsuperscript{52} Among the various drug delivery systems, microemulsion is considered an ideal alternative for oral delivery of poor water-soluble compounds.\textsuperscript{53} They have several advantages including ease of preparation, low viscosity, thermodynamic stability, enhanced dissolution of lipophilic drugs and bioavailability improvement.\textsuperscript{54,55} Furthermore they can be administered through different routes such as transdermal, parenteral, pulmonary and ocular.\textsuperscript{56} Ali et al.\textsuperscript{57} developed a novel microemulsion-based gel formulation of babchi oil (Psoralea coryfolia). Similarly, Wang et al.\textsuperscript{58} made an attempt to enhance anti-inflammatory activity of curcumin by formulating it into nanoemulsion. In order to reduce the toxicity of triptolide, Chen et al.\textsuperscript{56} studied microemulsion systems for transdermal delivery. Microemulsion preparations are further presented in Table 4.
Conclusion
Herbal drugs have been recently getting more attention because of their potential to treat almost all diseases. However, several problems such as poor solubility, poor bioavailability, low oral absorption, instability and unpredictable toxicity of herbal medicines limit their use. In order to overcome such problems, nanoparticles can play a vital role. Hence, different nanoparticles including polymeric nanoparticles, liposomes, proliposomes, solid lipid nanoparticles and microemulsions showcase potential utilization to deliver herbal medicines with better therapy.

References

22. Yen FL, Wu TH, Lin LT, Lin CC. Hepatoprotective and antioxidant effects of Cuscuta chinensis against

Table 4: Microemulsion herbal formulations

<table>
<thead>
<tr>
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<th>Benefit of formulation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furocoumarin Psoralen</td>
<td>Occurs naturally in the seeds of Psoralea corylifolia</td>
<td>Treatment of skin diseases characterized by hyperproliferation such as psoriasis</td>
<td>-</td>
<td>Enhanced anti-inflammatory effects</td>
<td>57</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Natural polyphenol isolated from the root of Curcuma longa</td>
<td>Antitumor, antioxidant, antiplatelet aggregation and anti-inflammatory</td>
<td>61.8-79.5 nm</td>
<td>Enhanced anti-inflammatory effects</td>
<td>58</td>
</tr>
<tr>
<td>Triptolide</td>
<td>Diterpenoid triepoxide obtained from traditional Chinese medicine Tripterygium wilfordii Hook F</td>
<td>Used in the treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia and anti-neoplastic activity</td>
<td>71.1 nm</td>
<td>Reduction in toxicity of triptolide following transdermal delivery</td>
<td>56</td>
</tr>
</tbody>
</table>


