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Status of novel drug delivery technology for phytotherapeutics

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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. However, phytotherapeutics needs 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 for herbal constituents. Novel drug delivery systems 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, and so on. Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach. 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 systems. However, modern phytopharmaceutical research solves the scientific needs for herbal medicines as in modern medicine, which gives way for developing novel formulations such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles, and so on. This article summarizes various drug delivery technologies for herbal actives, which are gaining more attention for better therapeutic response.

Keywords: cardiac stents, herbal medicines, liposomes, matrix system, microemulsion, polymer conjugation, polymeric nanoparticles, proliposomes, solid dispersions, solid lipid nanoparticles, tissue engineering, transdermal patches

Expert Opin. Drug Deliv. (2009) 6(6):625-637

1. Introduction

Phytotherapy has been practised for thousands of years all over the world and has been an important part of ancient culture in countries such as India, China and Egypt. In recent decades the use of phytotherapeutics has increased significantly among patients and physicians as is evident from an increased market for herbal medicines [1]. The global market for herbal medicines or plant-derived drugs is expected to increase from $18 billion from 2005 to $26 billion by 2011 [2]. The other reason for an increase in market share is the introduction of herbals in the form of dietary supplements and nutraceuticals [3,4]. However, the formulation of herbal medicines into novel dosage forms is slow owing to the complexity of the active constituents. Although several formulations for herbal drugs have been developed and have been demonstrated to have efficacy similar to that of chemically synthesized modern drugs, a lot more investigation still needs to be done. Herbals having one constituent in novel drug delivery formulations are listed in **Table 1**. The activity of the herbal medicines depends on the overall function of a variety of active components, as all the constituents provide synergistic action and thus enhance the therapeutic value. Their nature serves us with the exact proportion of all the constituents for various ailments

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Table 1. List of herbals having monoconstituent in novel drug delivery formulations.

Monoconstituent herbal medicine	Chemical classification species	Pharmacological activity	Novel formulations	Ref.
Camptothecin	Cytotoxic quinoline alkaloid isolated from bark and stem of the oriental tree *Camptotheca acuminate*	Treatment of gastric, rectum, bladder, colon, lung, breast and ovarian cancers	Polymer conjugations, polymeric nanoparticles, liposome, solid lipid nanoparticles	[18,19,74,79,80]
Curcumin	Natural polyphenol isolated from the root of *Curcuma longa* (turmeric)	Antitumor, antioxidant, antiamyloidn, antiplatelet aggregation and anti-inflammatory	Microemulsions, cardiac stents, polymeric nanoparticles, liposomes, solid lipid nanoparticles	[13,34,43,51,67]
Hypericin	Anthracene glycoside occurring in *Hypericum perforatum*	Photosensitizer used in photochemotheraphy	Polymeric nanoparticles	[20]
Khellin	Furanochromone glycoside extracted from the seeds of *Ammi visnaga*	Used in the photochemotherapy of dermatoses such as vitiligo and psoriasis	Transdermal gel containing khellin	[59]
Tetrandrine	Bisbenzylisoquinoline alkaloid extracted from the roots of *Stephania tetrandria*	Anti-inflammatory, antiplatelet aggregation, antiarthritis, Ca^{2+} channel block, immunosuppressive and free radical scavenging and tissue regenerating agent	Albumin-loaded microparticles, scaffold and solid lipid nanoparticles	[44,73,81]
Triptolide	Diterpenoid triepoxide obtained from traditional Chinese medicine *Tripterygium wilfondil HookF*	Treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia by oral or intravenous route. Antineoplastic activity	Solid lipid nanoparticles, microemulsions, polymeric nanoparticles	[17,45,49]
Vincristin	Bisindole alkaloid obtained from the periwinkle *Catharanthus roseus* (Vinca rosea)	Broad spectrum anticancer against lung melanoma, ovarian, renal, prostate and breast carcinomas	Liposomes	[33,82,83]

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in a single species. Each active constituent plays an important role and they are all related to each other [5,6]. Herbals having more than one constituent in novel drug delivery formulations are listed in **Table 2**.

The drug targeting with NDDS to individual organs improves selectivity, drug delivery and effectiveness with dose reduction, and safety, and increases compliance. The requirements of an ideal drug carrier for NDDS are that it should be capable of extended circulation in bloodstream, and small enough to reach target cells and tissues and escape the reticuloendothelial system. Drug delivery leads to target organs directly delivering the active constituents in a predetermined manner. Drugs can be delivered to target sites such as the brain, lung, liver, kidney, pancreas, limbs, bladder, gastrointestinal tract, head and neck, breast and prostate [7,8].

Most of the herbal actives are poorly soluble and have a hydrophobic nature. The poor solubility and hydrophobic property of herbal actives lead to lower bioavailability and increased systemic clearance, requiring repeated administration or increased dose, as a result of which the clinical use of herbal medicines is limited. The imitations of herbals in clinical use are listed in **Table 3**. Novel formulations can be 'nano' or 'micro' particulate drug delivery systems or sustained release dosage forms containing various types of polymer or lipid carrier used to deliver the drug by various routes, including, for example, the transdermal, buccal, oral, parenteral routes. They help to localize the drug in a specific site and to bring better efficacy, and hence improve patient compliance. A list of novel drug delivery formulations of herbals reported in the literature is tabulated in **Table 4**. Some studies focusing on development of novel drug delivery systems for herbal drugs are listed as follows.

2. Polymeric nanoparticles

Nanoparticles (nanospheres and nanocapsules) are colloidal systems with particles varying in size from 10 to 1000 nm. A nanosphere is a matrix structure in which the active ingredient is dispersed throughout the particles, whereas nanocapsules have a polymeric membrane and an active ingredient in the core. Nanoparticles provide many advantages, such as solubility enhancement, thereby leading to bioavailability enhancement, reduction in dose, improvement in therapeutic effectiveness, better stability, and improved absorption of herbal medicines as compared with the respective crude drug preparations [9-11].

Sahu *et al.* [12] synthesized a new biodegradable and self-assembling polymer, methoxy poly(ethylene glycol)–palmitate,

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Table 2. List of herbals containing more than one constituent in novel drug delivery formulations.

Multiconstituent herbal medicines	Chemical classification species	Active constituents	Pharmacological activity	Novel formulation	Ref.
Catechins	Polyphenolic plant metabolites abundant in teas derived from the tea plant *Camellia sinensis*	(+)-catechin, (-)-epicatechin, (-)-epigallocatechin-3-gallate	Chemopreventive, anticarcinogenic, antiviral, antioxidative, anti-obesity, hypolipidemic, anti-inflammatory, apoptotic, hypocholesterolemic, antiarteriosclerotic, antidiabetic, antimutagenic, antiangiogenic, antibacterial and antiageing	Chitosan nanoparticles and liposomes	[28,35,36]
Silymarin	Flavonol glycoside obtained from dried fruits of *Silybus marianum*	Silybin, taxifolin, isosilybin, silydianin and silychristin	Hepatoprotective agent	Liposomes, proliposomes, solid dispersions, matrix tablets	[5,31,39]
Breviscapine	Bioactive flavonoid obtained from extracted *Erigeron breviscapus* (Vant.) Hand.-Mazz	Scutellarin	Used in ischemic cerebrovascular and cardiovascular diseases such as cerebral infarction, apoplexy, coronary heart disease and angina pectoris in injection preparation	Liposomes	[78]
Cuscuta chinensis	Obtained from Chinese herbal medicine *Cuscuta chinensis* Lam	Flavonoids and lignans such as quercetin, kaempferol	Used as tonic for the liver and the kidney Used to improve sexual function, prevent senescence and regulate the immune system. Some of the studies showed anticancer, antioxidant, antiageing and immuno-stimulatory effects of *Cuscuta chinensi*	Nanoparticles (nanosuspension)	[21]
Guarana	Purine alkaloids obtained from *Paullinia cupana* var. *sorbilis* (Mart)	Methylxanthine derivatives such as caffeine, theophylline and theobromine	Relaxation of smooth bronchial muscle, CNS stimulation, cardiac muscle stimulation and diuresis	Transdermal patch	[60]
Podophyllotoxin	Podophyllotoxin is the compound of resin mixture known as podophyllin obtained from the dried roots of *Podophyllum peltatum*	Podophyllin	Antivirus in the treatment of warts through topical application and anticancer	Polymer conjugations and solid lipid nanoparticles	[47,75]
Psoralen	Occurs naturally in ths seed of *Psoralea corylifolia*	Psoralens	Treatment of skin diseases characterized by hyperproliferation such as psoriasis	Microemulsions	[50]

Table 3. Imitations of herbals in clinical use.

Herbal medicine	Limitations in clinical use	Novel drug delivery formulation and route of administration for overcoming problems	Ref.
Multiconstituent herbals			
Catechins	Bioavailability is < 5% and the half-life of catechins is short owing to strong systemic clearance	Oral delivery of chitosan nanoparticles and transdermal liposomes	[28,35,36]
Silymarin	Poor absorption by oral administration owing to degradation in gastrointestinal tract, thereby reduced bioavailability. In addition possesses poor water solubility	Oral liposomes, proliposomes, solid dispersions, matrix tablets	[5,31,39]
Breviscapine	Shorter systemic circulation hence the mean residence is less	Injectable multivesicular liposomes	[78]
Cuscuta chinensis	Poor water solubility	Oral polymeric nanoparticles	[21]
Monoconstituent herbals			
Camptothecin	Poor water solubility and some toxic effects. After prolonged administration camptothecin can indeed result in neutropenia, thrombocytopenia, anemia and some non-hematological toxic effects such as alopecia, nausea, vomiting, diarrhea, fatigue and skin rash	Intravenous administration, biodegradable implants, hydrogel of polymer conjugations, polymeric nanoparticles, liposomes, solid lipid nanoparticles	[18,19,74,79,80]
Hypericin	High lipophilicity in physiologically acceptable media makes the systemic administration of conventional photosensitizer (hypericin) problematic and restricts their diagnostic applications	Intravenous, topical and oral administration of polymeric nanoparticles	[20]
Curcumin	Low solubility in aqueous solutions, which limits its bioavailability and clinical efficacy	Microemulsions, polymeric nanoparticles, liposomes, solid lipid nanoparticles were administered through intravenous, cream, cardiac stents	[13,34,43,51,67]
Khellin	On oral administration it has shown systemic adverse effects such as nausea and elevation of liver transaminases (hepatotoxicity)	Transdermal drug delivery system	[59]
Podophyllotoxin	Severe side effects after systemic absorption. Podophyllotoxin is insoluble and unpredictable in systemic behavior	Intravenous and epidermal delivery of polymer conjugations and solid lipid nanoparticles	[47,75]
Tetrandrine	Accumulates in the liver after oral administration and causes hepatic damage	Intravenous, inhaled delivery of albumin loaded microparticles, solid lipid nanoparticles.	[44,73,81]
Triptolide	Suffers from practical disadvantages owing to its poor water solubility and toxic effects. The adverse drug reaction was significantly higher than other drugs, including gastrointestinal, urogenital, cardiovascular, blood circulatory system, bone marrow as well as hypersusceptibility of skin	Transdermal delivery of solid lipid nanoparticles, microemulsion, polymeric nanoparticles	[17,45,49]
Vincristin	Neurotoxicity	Intravenous liposome delivery	[33,82,83]

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Table 4. Novel drug delivery formulations of herbals reported in the literature.

Novel drug delivery formulations	Herbal drugs
Nanoparticles and microparticles	Catechins, cuscuta chinensis, camptothecin, curcumin, hypericin, triptolide and tetrandrine
Liposomes and proliposome	Catechins, camptothecin, curcumin, silymarin, and vincristin
Solid lipid nanoparticles	Camptothecin, curcumin, tetrandrine, triptolide and podophyllotoxin
Polymeric conjugations	Camptothecin and podophyllotoxin
Microemulsions	Triptolide, babchi oil (psoralen)
Transdermal patches and gels	Guarana extract and khellin
Solid dispersion and matrix tablets	Silymarin
Polymeric cardiac stents	Curcumin
Scaffolds	Tetrandrine

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for curcumin delivery to cancer cells. Curcumin has pharmacological activity, including antitumor, antioxidant and anti-inflammatory properties [13]. It has been reported that it is also a potent inhibitor of carcinogenesis against a variety of cell lines such as prostate, pancreatic, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, breast and cervical cancer. As curcumin has very low solubility and bioavailability, its clinical use is restricted. Nanocarriers using methoxy poly(ethylene glycol) as the hydrophilic part, palmitic acid as the hydrophobic part and curcumin present in the core of the polymer micellar have been prepared. The prepared micellar nanocarriers were spherical in shape with mean diameter of 41.43 nm. The loading capacity of the curcumin increased as polymer conjugate increased; ~ 100% encapsulation was achieved. These nanocarriers increased the solubility and bioavailability of curcumin (i.e., the cytotoxicity assay showed that encapsulated curcumin inhibited cell proliferation comparably to free curcumin IC_{50} = 15.58 µm and IC_{50} = 14.32 µm, respectively) and reduced the toxicity, and thus can be used clinically for the treatment of cancer therapy as a chemopreventive agent [12].

In another study, triptolide-loaded poly(DL-lactic acid) nanoparticles were developed for the investigation of their anti-inflammatory activity. Triptolide has many activities, including immunosuppressive effects, anti-inflammatory, and so on, and also has disadvantages such as poor solubility and toxicity [14-16]. The nanoparticles were developed with biocompatible and biodegradable polymers, poly(DL-lactic acid) to overcome these problems. They were found to be uniform in size, spherical in shape, having a smooth surface and a narrow size distribution with mean particle size of 149.7 nm. An 85.7% encapsulation efficacy was achieved. The drug release from the nanoparticles followed biphasic mechanism, that is, initial burst release followed by slow release [17].

It has been found that the active lactone ring in the camptothecin is readily hydrolyzed in physiological condition, that is, in pH 7.4 at 37°C and in the bloodstream, with the result that the hydrolyzed yield compound is less active and is converted into highly toxic open ring carboxylate form. Min *et al.* [18] developed hydrophobically modified glycol chitosan nanoparticle-encapsulated camptothecin for targeting tumor and for better stability. The hydrophobic 5β-cholanic acid moiety was chemically conjugated with hydrophilic glycol chitosan backbone and camptothecin was encapsulated for intravenous administration. The encapsulation efficiency was found to be 80% and the particle size was in the range 280 – 330 nm. The formulation was stable and was protected from hydrolysis of active lactone ring of camptothecin in physiological environment with sustained release over a period of 1 week in blood circulation. The preparation showed better tumor targeting and antitumor ability towards human breast cancer xenografts after intravenous injection. In another study a novel polymeric microparticle of camptothecin using poly(DL-lactic-*co*-glycolic acid) was developed for tumoral treatment and to overcome poor solubility and instability problems. The developed microparticles increased the solubility and showed sustained release and stability of the medicament over a period of 25 days. The particle size was ~ 32 – 38 µm with encapsulation close to ~ 100% [19].

An attempt was made for photodetection and photodynamic therapy using polymeric-loaded nanoparticles of hypericin, a natural photosensitizer extracted from *Hypericum perforatum* for the early diagnosis of ovarian cancer. Hypericin is a highly lipophilic or insoluble agent in physiologically acceptable media and therefore makes the systemic administration of conventional photosensitizer (hypericin) problematic and restricts its diagnostic applications. To overcome these problems, an injectable suspension of polymeric nanoparticles with hypericine was developed using biodegradable and biocompatible synthetic polymers such as polylactic acid (PLA) or polylactic-*co*-glycolic acid (PLGA) for better photodetection and photodynamic therapy for the early diagnosis of cancer. The prepared nanoparticles of hypericin were in the size range 200 – 300 nm and up to 70% encapsulation efficiency was achieved. The nanoparticles prepared with PLA showed better *in vitro* activity than those prepared with PLGA [20].

Yen *et al.* [21] developed nanoparticles of *Cuscuta chinensis* by a nanosuspension method to evaluate hepatoprotective and antioxidant activity in rats. *Cuscuta chinensis* is known to have activities such as hepatoprotective, anticancer, antiageing and immunostimulatory activities [22-27]. It has limited absorption through an oral route owing to poor water solubility, hence clinical use is limited. Nanoparticles were developed to enhance solubility with particle size of ~ 267 nm, narrow size distribution and small spherical shape and 90% encapsulation efficiency of its constituent quercetin.

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Zhang and Kosaraju [28] studied a biopolymeric delivery system for controlled release of catechin (polyphenolic antioxidant). In the study, chitosan was used as the encapsulating material because it is recognized as being biodegradable, biocompatible and mucoadhesive. Catechins have pharmacological properties, including antioxidative, anti-inflammatory, antimutagenic, anticarcinogenic, antiangiogenic, apoptotic, antiobesity, hypocholesterolemic, antiarteriosclerotic, antidiabetic, antibacterial, antiviral and antiageing effects [29]. The antioxidant activity of catechin is decreased dramatically when it is introduced in an alkaline environment as in the human intestine. Therefore, it needs to be protected from the alkali attack [30]. The prepared chitosan-encapsulated catechin particles were in the mean size range 1.97 – 6.83 µm with entrapment efficacy of 27.9 and 40.12% depending on the polymer ratio. The *in vitro* release showed that not more than 50% showed up to 80% protection from an alkali environment.

3. Liposomes

Liposomes have been developed since 1970 for drug delivery to a specific site in the body [31]. The amphiphilicity of the vesicle and biocompatible and biodegradable nature are promising for drug delivery of herbal drugs. The advantages include improvement of therapeutic activity and safety of drugs, increased bioavailability, sustained release action and local delivery of medicament at the site of action [32]. In cancer therapy the liposome-encapsulated anticancer drugs have shown increased activity and reduced toxicity as compared with the free drug [33].

Sou *et al.* [34] developed a modified nano-lipid vesicle loaded with curcumin to deliver it into tissue macrophages through intravenous injection. Macrophages are related with different diseases associated with inflammation and have the property to protect cells and tissue from oxidative stress. To investigate the antioxidant ability and tissue macrophages' distribution, curcumin was encapsulated into a phospholipid vehicle comprising 1,2-dimyristoyl-*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 and was given intravenously to rats. It was found to be massively distributed in cells assumed as macrophages into the bone marrow and spleen. Thus, this vehicle can be used to provide improved intravenous delivery of curcumin to tissues' macrophages, specifically bone marrow and splenic macrophages for potential therapy in antioxidant and anti-inflammatory treatment.

Fang *et al.* [35] studied liposomal formulations encapsulating tea catechins possessing antioxidant and chemopreventive activities. *In vitro* and *in vivo* skin permeation studies were done using nude mouse skin model for transdermal delivery. The study showed appreciable permeation of (+)-catechin when encapsulated in liposome formulated with anionic surfactant deoxycholic acid and dicetyl phosphate in the presence of 15% ethanol. Among chatechins, (-)-epigallocatechin-3-gallate had the highest loading rate and *in vivo* skin deposition among all the catechins tested.

Lee *et al.* [36] developed calcium pectinate gel beads (CPG) entrapping catechin-loaded liposomes for oral sustained delivery because catechins are rapidly absorbed, excreted faster and their duration in plasma is shorter. The formulation was compared with free catechin loaded in calcium pectinate gel beads and the influence of hydroxypropyl methylcellulose (HPMC) on release was also examined. The entrapment efficiency was found to be 70% with 2% calcium chloride, indicating that the CPG beads with liposome and HPMC can be used for sustained oral delivery of catechins for health-promoting functions such as antioxidative, antiobesity, hypolipidemic and anticarcinogenic properties.

Samaligy *et al.* [31] increased the bioavailability of silymarin (antihepatotoxic agent) using a buccal liposomal delivery system. They worked with the hypothesis that liposomal dosage form intended for buccal delivery provides the desired bioavailability with lower dose for the treatment of liver diseases in children. The result showed greater encapsulation (70%) and the formulation was stable for 3 months at 4°C with stearyl amine as a positive charge inducer. *In vitro* permeation studies resulted in better permeation for formulation composed of lecithin:stearyl amine:cholesterol:Tween 20 in 9:1:1:0.5 molar ratio compared with free silymarin.

4. Proliposomes

The liposomes possess many advantages for drug delivery; however, they also have some disadvantages, for example, physicochemical instability such as aggregation, sedimentation, fusion, phospholipid hydrolysis and/or oxidation and problems in sterilization and large-scale production. To overcome these problems with liposomes, a novel method of producing liposomes has been reported, called proliposomes [37,38]. Proliposomes are defined as dry, free-flowing particles that immediately form a liposomal suspension when in contact with water. Owing to the solid properties of proliposomes, the stability problems of liposomes can be resolved without influencing their intrinsic properties. Proliposomes can be formulated by methods such as film-deposition on carriers, the crystal-film method, powder bed grinding, the fluid-bed method, and freezing and drying and spray drying methods [39].

A study was conducted by Yan-yu *et al.* [39] in beagle dogs to study the oral bioavailability of silymarin encapsulated into proliposome. Silymarin suffers from poor permeability across the intestinal epithelial cells and has limited absorption in the gastrointestinal tract [40,41]. Silymarin proliposomes were formulated by film-deposition on carriers, which was found to be stable for 3 months at 40°C with > 90% of encapsulation efficiency and mean particle size of 196.4 nm. The bioavailability studies indicated improved bioavailability of silymarin in proliposome form as compared with pure silymarin.

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5. Solid lipid nanoparticles

Solid lipid nanoparticles (lipospheres or solid lipid nanospheres) are of submicrometer size (50 – 1000 nm) made from lipids that remain in a solid state at room temperature and body temperature. They consist of lipids including lipid acids, mono-, di-, or triglycerides, and glyceride mixtures or waxes, and are stabilized by the biocompatible surfactants. The advantages of solid lipid nanoparticles (SLNs) are the possibility of controlled drug release and drug targeting, protection of incorporated compound against chemical degradation, decrease of the drug toxicity, good tolerability, biodegradation, increased bioavailability, no biotoxicity of the carrier, avoidance of organic solvent, incorporation of lipophilic and hydrophilic drugs and no problems with respect to large-scale production and sterilization. The formulations incorporating herbal drugs in SLNs include mouthwashes (e.g., peppermint oil), gargles (e.g., thymol) and inhalations (e.g., eucalyptus oil) [42-44].

Mei *et al.* [45] studied the anti-inflammatory activity and transdermal delivery capacity of triptolide by developing it into novel solid lipid nanoparticles and a microemulsion formulation. The SLN formulation consisted of 5% tristearin glyceride, 1.20% soybean lecithin and 3.60% polyethylene glycol (400) monosterate. The microemulsion formulation consisted of 40% isopropyl myristate, 50% Tween 80:1,2-propylene glycol (5:1 v/v) and water. Both the formulations showed very good transdermal permeation and anti-inflammatory effect in the case of carrageenan-induced rat paw edema and Freund's adjuvant-induced paw edema. The particle size of SLN was < 200 nm, which showed both burst release and sustained release drug profile. The burst release can be useful to promote drug penetration transdermally and a sustained effect helps to prolong the dose release for anti-inflammatory activity for a longer time. In other study, Mei *et al.* tried to reduce the hepatotoxicity induced by triptolide and improved its anti-inflammatory activity by formulating triptolide into SLNs. The SLN form showed stronger anti-inflammatory effect than free drug with oral administration of free triptolide, indicating that SLN formulation had the capability of protecting liver from necrosis [46].

Chen *et al.* [47] studied podophyllotoxin-loaded solid lipid nanoparticles (POD SLNs) targeting epidermis for the treatment of genital warts. Podophylotoxin acts by inhibiting the growth of epithelial cells infected by the human papilloma virus. In this study, POD SLNs were developed to accumulate in the epidermis and prevent systemic absorption to overcome the disadvantages of an ordinary tincture and cream formulation, which tends to absorb systemically and cause dermal irritation. POD SLNs were formulated by a high-pressure homogenization method with an average diameter of 73.4 nm and zeta potential of –48.36 mV. Penetration was found through the stratum corneum and hair follicle route with sustained effect. The POD SLNs formulated with 1.5% soybean lecithin were found to accumulate more in the epidermis than the formulation prepared with 2% polysorbate 80. POD SLNs can be a promising drug delivery system for better therapy and can reduce adverse effects caused by systemic absorption.

Tiyaboonchai *et al.* [43] 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. The decomposition was pH-dependent and stable at pH < 6.5. More than 50% of degradation was observed in the model cream formulation of curcuminoid after 3 months' storage. To overcome this problem, Tiyaboonchai *et al.* have developed a novel curcuminoid-loaded SLN incorporated into cream. An optimized formulation with an average particle size of 447 nm and 70% encapsulation released the drug for 12 h and was stable for up to 6 months as compared with free curcuminoid cream formulation. It was found that cream loaded with SLN curcuminoid showed a marked reduction in skin wrinkles and improved skin moisture and viscoelasticity after application for 3 weeks.

The traditional Chinese medicine tetrandrine has been clinically used to treat arthritis, silicosis, hypertension and fibrosis. To modernize the traditional Chinese medicine, Li *et al.* [44] have developed SLN of tetrandrine as it is highly lipophilic. Ultrasonication was used to formulate tetrandrine SLN with an average particle size of 157.3 nm, –29.36 mV and encapsulation efficiency of 90.59%.

6. Microemulsion

Microemulsion is defined as 'a system of water, oil and amphiphile that is a single optically isotropic and thermodynamically stable liquid solution' [48]. Microemulsion is also defined as 'a dispersion consisting of oil, surfactant, co-surfactant and aqueous phase, which are a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10 – 1000 nm'. Microemulsions have several advantages, such as enhanced drug solubility, good thermodynamic stability, ease of manufacturing, optical clarity and have excellent kinetic stability, Furthermore, they can be administered through a range of routes, such as transdermal, parentral, pulmonary and ocular [49].

Ali *et al.* [50] have developed a novel microemulsion-based gel formulation of babchi oil (*Psoralea corylifolia*). Babchi oil mainly contains a major photoactive furocoumarin psoralen that acts by binding DNA and inhibits DNA synthesis and causes a decrease in cell proliferation in the presence of UV light in the treatment of psoriasis. Microemulsions were prepared by an aqueous phase-titration method with a droplet size of 78.53 nm and 73.23 cps viscosity. The optimized formula contained 1.67% v/v of babchi oil, 8.33% v/v of oleic acid, 55% v/v of Tween 80 Transcutol-P (S/Co ratio 1:1) and 35% v/v of distilled water and was made as a gel formulation using 1% carbopol-940. *In vivo* anti-inflammatory effects determined by footpad edema showed better action of babchi oil micremulsion than the marketed ordinary babchi oil.

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Microemulsion gel has potential for topical delivery of psoralen present in babchi oil in the treatment of psoriasis.

Wang *et al.* [51] have made an attempt to enhance anti-inflammatory activity of curcumin by formulating it into O/W (water in oil) nanoemulsions by a high-speed and high-pressure homogenization method. The optimized formulation had mean droplet sizes ranging from 618.6 to 79.5 nm. These formulations were compared with 1% curcumin in 10% Tween 20 water solution against 12-*O*-tetradecanoylphorbol-13-acetate-induced edema of mouse ear and it was found that microemulsions prepared by a high-pressure homogenization method showed increased activity compared with those prepared using a high-speed method, that is, 43% and 85% and no inhibition was seen with 1% curcumin in 10% Tween 20 water solution.

To reduce the toxicity of triptolide, Chen *et al.* [49] studied microemulsion systems for transdermal delivery of triptolide. Microemulsion formulation containing triptolide 0.025%, oleic acid 6%, Tween 80 20%, propylene glycol 10%, water 62.950% and menthol 1% (as permeation enhancer) had an average particle size of 71.1 nm and showed better protection from irritation for 7 days after application. However, a simple formulation with 20% propylene glycol containing 0.025% triptolide caused erythema and edema. This novel microemulsion formulation for the transdermal delivery of triptolide can be advantageous.

7. Solid dispersions

Solid dispersion techniques have been widely used as a means of improving the dissolution rate and oral bioavailability of poorly water soluble drugs [52,53]. Solid dispersion can be prepared by two methods, such as the melting method and the solvent method. The melting method involves the melting of drugs and carriers with a low melting point such as polyethylene and subsequent cooling and congealing at low temperatures. The solvent method is used for high melting point carriers, which involves the solubilization of drugs together with carriers in a suitable solvent followed by evaporation of the solvent under a reduced pressure [54-58].

Silymarin (SM), an antihepatotoxic herbal medicine, possesses poor water solubility leading to low oral bioavailability and restricted commercial application. To overcome this problem, Sun *et al.* [58] developed silymarin solid dispersions to enhance its dissolution rate thereby increasing its oral absorption and oral bioavailability. Silymarin solid dispersion pellets were formulated by a one-step fluid-bed coating technique. The optimized ratio of polyvinylpyrrolidone (PVP):SM 4:1 and 5:1 with 80 and 120% weight gain showed a better dissolution profile of ~ 60% at 5 min and 80% at 10 min, which was 10 times more compared with simple silymarin powder. It was also found that increased concentration of PVP (PVP:SM 6:1) decreased the dissolution rate owing to the prevention of water permeation inwards. The overall result suggests that the fluid-bed coating technique of silymarin solid dispersions over non-pareils pellets can be used for manufacturing commercially.

8. Transdermal patches and topical gels

Delivery of herbal active compounds through the skin is an alternative to oral, intravenous and other routes of administration. The advantages include avoidance of the first pass effect, sustained therapeutic action, constant plasma concentrations and reduced side effects owing to lower doses and better patient compliance. Transdermal patches are one of the novel dosage forms applied for delivering the drug through the skin with the help of physical or chemical penetration enhancers to overcome the protective barrier of the stratum cranium for drug passing through skin. The physical methods include ultrasound, iontophoresis, electroporation, magnetophoresis and micro- and nano-needle, whereas the chemical enhancers are sulfoxides, azones, glycols, alkanols and terpenes. The other approaches for delivering the drug through the skin are nanocarriers such as polymeric nanoparticles and lipid nanoparticles such as liposomes, microemulsions, solid lipid nanoparticles, and so on. The nanocarriers have the property of penetration through skin without any penetration enhancer or penetration techniques when they have a particle size < 200 nm [59,60].

Khellin (furanochromone derivative) extracted from the seeds of *Ammi visnaga* is used in the treatment of vitiligo and psoriasis. When given orally it results in nausea and hepatotoxicity. Marconi *et al.* [59] studied the passive and ionotophoretic drug passage of khellin into skin using gel formulations, for effective treatment in skin disease. Two types of gel were formulated with and without a conductivity component (NaCl) for transport study, namely passive and ionotophoresis methods, respectively. The accumulation of khellin in all the layers of skin was observed through passive transport. However, passive transport needs more application time, whereas after application of gel on skin, a current was applied (inotophoresis) for better permeation and the result showed that khellin was able to permeate through the stratum corneum to reach the basal epidermis and upper dermis with a much shorter application time. Thus, a combination of passive and ionotophoretic techniques could serve for drug distribution in the skin, especially in dermal treatment avoiding systemic reach of the drug.

Heard *et al.* [60] studied transdermal delivery of caffeine, theobromine, theophylline and catechin from extract of guarana (*Paullinia cupana*), which had a CNS stimulatory effect. Different guarana extracts ranging from 0.09 to 10.78 mg/patch were incorporated in a readymade patch Duro-tak® 387 – 2287 (drug-in-glue patches; National Starch and Chemical Co., USA) and compared with a commercially available transdermal patch for release of all the components simultaneously. The administration of all major active substances of guarana has stimulatory effects of caffeine rather than caffeine alone. The study concluded that the commercially available patches

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containing lower amounts of guarana are unable to deliver adequate amounts of the lesser components across the skin.

9. Cardiac stents and drug delivery

Drug-eluting stents with biodegradable and biocompatible polymer coating that release antiproliferative drugs such as rapamycin and paclitaxel have opened up a new paradigm in cardiac treatment [61-63]. The reason for and advantages of polymeric coating is that they can achieve high local drug concentration [64,65] over a period of several weeks or months by controlling release or sustaining release of drug [66].

Pan *et al.* [67] prepared curcumin-eluting controlled biodegradable coating stents for anticoagulation activity in the treatment of in-stent restenosis. The stents were prepared by spraying 1% biodegradable polymer PLGA containing curcumin on 316L stainless steel stent in different dose levels. The *in vitro* release studies showed a sustained release profile of curcumin over a period of 18 days. The *in vitro* anticoagulation activity of prepared PLGA curcumin stent was measured by platelet adhesion measurements and activated partial thromplastin time tests. These showed that coagulation of blood was suppressed by curcumin release from the drug-eluting stent. Increasing the dose of curcumin resulted in prolonged anticoagulation activity, thus preventing thrombus formation after stent implantation.

10. Matrix system

Tablets compressed with hydrophilic matrices are usually used as oral drug delivery systems because they provide controlled blood levels, good compatibility, sustained release dose delivery and reduced dosing frequency. They resulted in the release of drug at appropriate rate to maintain suitable plasma drug levels for therapeutic efficacy. The hydrophilic matrix controls the drug release from the tablet by forming a hydrated viscous or gel layer around it, which acts as a barrier to drug release by opposing penetration of water into the tablet and also movement of dissolved solutes out of the tablet. The mechanism of drug release from the matrix tablet is influenced by the polymer, as the matrix swelling, erosion and diffusion of drug determine the kinetics and the physical and mechanical properties of the gel barrier that forms around the tablet [68-70].

Lu *et al.* [5] studied synchronized and sustained release of multiple components in silymarin from an erodible glyceryl monostearate (GSM) matrix system and compared it with HPMC K4M matrix formulation. HPMC matrix tablets were formulated by a direct compression method and melt fusion method to form a glyceryl monostearate matrix system, and drug release was compared from both the matrix systems against synchronized and sustained profiles of five components (taxifolin, silychristin, silydianin, and silybin and isosilybin) present in silymarin. The *in vitro* dissolution results indicated that HPMC matrix tablets released five components of silymarin in a sustained release manner. In the case of glyceryl monostearate/PEG 6000 (15/85), the matrix system released the five components that were released in sustained manner and followed synchronized release in the same manner. The optimal drug/polymer ratio was 1/20 and it showed synchronized release irrespective of the actual amount with sustained profile. This matrix system provided synchronized release of all five components from silymarin and could be a promising drug delivery system.

11. Tissue engineering and drug delivery

Scaffolds are an architectural context in which extracellular matrix, cell–cell and growth factor interactions combine to generate regenerative niches [71]. Scaffolds are used in tissue engineering, and aim to replace or facilitate the regrowth of damaged or diseased tissues by applying a combination of biomaterials, cells and bioactive molecules [72]. Controlled drug delivery is possible to deliver the drug to support and stimulate tissue growth in tissue engineering. The controlled release kinetics of the growth factor or drug from the scaffold is dependent on the porous structure of the scaffold and the porosity should be higher to deliver the growth factor. These scaffolds can be made by natural polymers (alginate, collagen, chitosan, gelatin and hyaluronan), synthetic polymers (polyacrylates, polyesters polyaminoamides, and their copolymers) and blends or hydrogel matrices (poly(ethylene glycolide), poly(vinyl alcohol) etc.) with physically or chemically crosslinked water-soluble polymers can also be used [71].

Tetrandrine possesses an anti-inflammatory, antiplatelet aggregation, Ca^{2+} channel blocking, immunosuppressive, free radical scavenging effect and is also used in tissue regeneration. Yan *et al.* [73] prepared controlled release porous scaffolds for tetrandrine, which can be used to promote chondrocyte differentiation and secrete type II collagen in tissue engineering by modifying poly(lactic acid) scaffold. The lipophilic bioactive component tetrandrine was entrapped in poly (L-lactide)-*b*-poly (methoxy ethylene glycol) nanoparticles with a particle size of 60 nm and embedded in chitosan–gelatin scaffolds. The tetrandrine release was sustained and was smoother from Cs–Gel–PLAE–Ted (chitosan–gelatin-poly(L-lactide)-*b*-poly(methoxy ethylene glycol)–tetrandrine) than Cs–Gel–Ted (chitosan–gelatin–tetrandrine) scaffolds without any initial burst release. The novel drug delivery approach of delivering bioactive herbal drug moiety from porous scaffold can serve as a good therapy in tissue engineering.

12. Polymeric conjugation

A novel polymer conjugation technique (polymer–bound) offers a valid method for enhancing the activity of herbal drugs such as camptothecin and phodophyllotoxin for better therapeutic effect by reducing *in vivo* toxicity and increasing water solubility. In this technique active drug can be synthetically modified by covalently attaching with a desirable polymer for controlled delivery as well as improved activity.

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Camptothecin is a potent antitumor drug that acts by inhibiting topoisomerase I during the S-phase of the cell cycle. However, its use has been clinically restricted owing to its unpredictable toxic effect. To overcome this problem, Caiolfa *et al.* [74] synthesized solible *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymers containing camptothecin 5 wt% and 10 wt%. After intravenous administration of camptothecin-conjugates in mice, plasma levels confirmed the modest hydrolysis in plasma. The plasma level of camptothecin conjugates was fivefold lower than camptothecin administered in classical vehicles. This polymer conjugate offers sustained release as well as reduced toxicity of camptothecin *in vivo*.

Podophyllotoxin is obtained from the dried roots of *Podophyllum*. It is used as a topical application in viral conditions such as Condyloma acuminatum (venereal warts). Podophyllin acts by inhibiting nucleoside transport into mammalian cells. The undesirable property of this compound is that it is insoluble in nature and results in unpredictable systemic behavior, limiting its clinical use. A study was carried out for chemical modification of podophyllin conjugating with soluble polyethylene glycol. These polymer conjugations resulted in better activity in the murine leukemia model compared with simple podophyllotoxin suspended in an intralipid emulsion [75].

13. Miscellaneous

Some herbal constituents are also used to enhance the drug delivery applications. These herbs alter the release of drug in the human body in a predetermined manner. Some of the naturally occurring constituents that have been used as crosslinking agents and permeation enhancer in drug delivery formulation have been discussed.

Genipin is a naturally occurring crosslinking reagent used in herbal medicine as antiphlogistic and cholagogue obtained from the parent compound geniposide isolated from the fruits of *Gardenia jasminoides*. Genipin is about 5000 – 10,000 times less cytotoxic than glutaraldehyde as a crosslinking agent. The study was undertaken by Mi *et al.* [76] to evaluate the feasibility of using genipin as a crosslinking agent to prepare injectable chitosan microspheres. The results showed that the degradation rate and degree of inflammatory reaction surrounding the tissue implanted with the genipin-crosslinked chitosan microspheres were less than in that implanted with the glutaraldehyde-crosslinked chitosan microspheres. Thus, genipin can be used as a crosslinking agent for polymers used in drug delivery technology.

Aqil *et al.* [77] reported that terpenes were found to be safe and effective penetration enhancers used in transdermal drug delivery systems, possessing no skin toxicity or irritation. These naturally occurring compounds (menthol, limonene, ascaridole, linalool, cineole, nerolidol, farnesol, geraniol, carvone) had the ability to permeate lipophilic as well as hydrophilic drugs through skin. Thus, terpenes can be used as permeation enhancers in several therapeutic classes of drugs formulated for topical treatment as well as systemic drug release.

14. Conclusion

Herbal drugs have the potential to treat all diseases with one or more active constituents present in them. Separating or isolating the most active constituent from the plant needs a lot of effort, time and money. After isolation of the active component, its chemical synthesis and large-scale production take several years. After chemical synthesis, its safety and efficacy (preclinical) in animals and in human (clinical) subjects need to be established, for which, again, several years are needed. To avoid this, attempts have been made to formulate herbal drugs in different dosage forms, such as tablets, capsules, syrups, cream, and so on. However, most drugs of plant origin possess poor solubility, poor bioavailability, low oral absorption, instability and unpredictable toxicity, which cannot be solved by classical formulations. To overcome all these problems of classical herbal formulations, the development of novel drug delivery systems for these phytodrugs may have potential in the future to bring about better therapy.

15. Expert opinion

Recently, herbal drugs have been getting more attention among scientists for the development of formulations, either classical or novel dosage forms. Moreover, the large-scale production of these drugs has also been increased significantly by several companies. This is because the market for herbal drugs is rising drastically and there has been a growth of awareness among people about the safety of plant origin drugs in developed and developing countries. Human clinical trials have increased for polyherbal drugs in all parts of the world, especially in India, for establishing the safety and efficacy of herbal medicines that have been prescribed for > 1000 years. These clinical trials are conducted to prove the safety of herbal medicines scientifically and it is most important for the companies to enter the global market and to sustain the competition. However, these products suffer from some biologically orientated problems, such as poor bioavailability and toxicity, for which novel drug delivery technology offers a wide range of advantages for plant origin drugs, mainly enhancement of pharmacodynamic, pharmacokinetic activities and reduction of toxicity. The future of the drug delivery market has been increasing rapidly since the drug delivery technology has become an integral part of pharmaceutical product development research and many companies have started developing new strategies for delivering drugs for site-specific organs. The pharmaceutical companies have started focusing on adopting new drug delivery technology for existing drugs, for various reasons, such as reducing the

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dosing frequency to meet patient compliance, and these developed products are normally filed as new drug application (NDA) to capture the generic market because the development of investigational new drugs (IND) is slow and developing new drugs for specific diseases takes a long time. To overcome this problem, nature serves herbs as medicines for all diseases. The combination of drug delivery technology and herbal medicines provides a safe and effective therapy for human beings.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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