REVIEW ARTICLE

Application of Novel Drug Delivery System in Enhancing the Therapeutic Potential of Phytoconstituents

Dilpreet Singh

Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India

Abstract

Various phytoconstituents obtained from nature have wide biological activities in chronic diseases and have wide therapeutic efficacy. The main advantage of using phytoconstituents is it provides free from adverse effects treatment where none of the medication can do. However, the physiochemical properties such as poor solubility, poor permeation, and non-targeting at the active site will create a barrier which hinders its therapeutic efficacy. So, various nanoformulation strategies are employed to overcome these barriers and provide uniform drug targeting at the active site in desired concentration and improved therapeutic efficacy. These strategies will constitute novel drug delivery systems (NDDS), such as nanoparticles, emulsion-based formulations, liposomes, phytosomes, microspheres, and topical based formulations, are available in commercial level to enhance the bioavailability of the poorly soluble herbal drug. In this review, we highlighted some novel applications of NDDS based approaches for enhancing the therapeutic potential of phytoconstituents having wide biological activities.

Key words: Nanoparticles, novel drug delivery system, phytoconstituents, phytosomes

INTRODUCTION

In modern drug discovery era, various chemically synthesized new molecules are approved by FDA and are coming on the market, having wide therapeutic efficacy, but the adverse effects are associated with this therapy causes serious adverse effects which could be life threatening. Conventional therapy provides non-targetability in tissues and organs due to peak and valley fluctuations, and a frequent dose of administration can produce troublesome for allopathic medicines lead to poor patient compliance.[1] The controlled release drug delivery system provides drug release at a controlled rate and maintains the overall therapeutic concentration of the drug in the body**.** In ancient times, herbal remedies and natural extract are consumed by people to cure various diseases. These herbal remedies contain hundreds of phytoconstituents present, which is working simultaneously against the disease. In recent times, the interest of people in phytopharmaceuticals has been increasing day-by-day among physicians and patients, and it is evident from the global market of herbal medicine and phytopharmaceuticals that has increased from $18 billion from 2005 and $26 from 2011.[2-4] Various dietary products and supplements are also derived from the natural origin are also gaining more interest in the industry and the global market for phytopharmaceuticals. Some phytoconstituents derived from the natural origin are having a poor solubility and low bioavailability resulting in a narrow therapeutic index, which hinders his novel efficiency, so formulation scientist is working on targeting and controlled drug release of phytoconstituents to provide better therapeutic effect and increased patient compliance.[5,6]

The three main goals of novel drug delivery system (NDDS) is by providing sustained drug release, selected targeting to the site of action and increased patient compliance [Figure 1]. NDDS not only reduce the frequency of administration but also reduce the Peak and valley fluctuations which lead to enhanced bioavailability. The applications of NDDS in phytopharmaceuticals have been widely investigated, and various commercial formulations of phytoconstituents are available in the global market which people will consume

Address for correspondence:
Dilpreet Singh, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar - 143 005, Punjab, India. E-mail: dilpreet.daman@gmail.com

Received: 09-08-2015
Revised: 22-10-2015
Accepted: 03-11-2015

and take benefit from it. In Phytoformulation research, various drug delivery vehicles, such as liposomes, polymeric nanoparticles, microemulsion, microspheres, solid lipid nanoparticles (SLNs), are used in which phytoconstituent is solubilized and release the drug in a sustained manner.[7-12] The list of drug delivery vehicles used in illustrated in Figure 2. In this review, we highlighted all the important applications of all the nanocarriers for controlled drug delivery of phytoconstituents [Table 1].

LIPOSOMES

Liposomes are discovered in 1970 as drug delivery vehicles for targeting at the active site into desired concentration. These are concentric bilayer vesicles in which the aqueous volume is entirely closed by lipid bilayer mainly composed of phospholipids [Figure 3]**.** Liposomes are biocompatible, non-toxic, and biodegradable in nature; hence, it is widely used in enhancing the therapeutic efficacy of various phytoconstituents. The advantages of liposomes in herbal formulations are given below.[13-15]

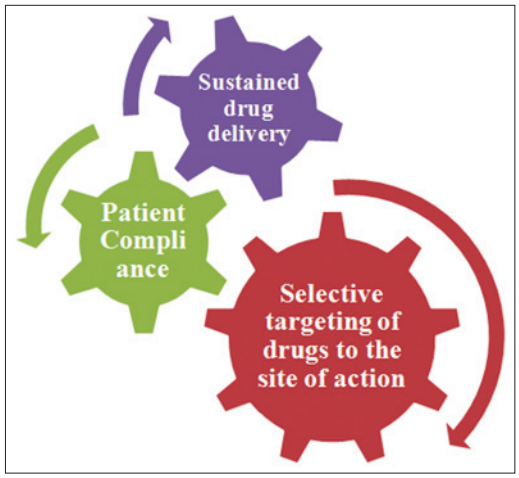

Figure 1: Goals of novel drug delivery system

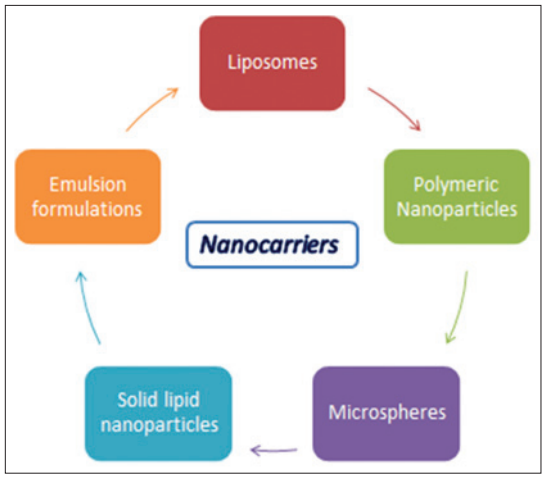

Figure 2: Novel drug delivery carriers in herbal formulations

- Provides herbal drug release in a sustained fashion
- Reducing peak-valley fluctuations
- Targeting of herbal drug into the desired area
- Improving the solubility and bioavailability of hydrophobic drugs.

There are various methods to prepare liposome-like thin film hydration method, mechanical dispersion method, and rotary film evaporation method. The method is selected based on various factors such as drug loading capacity, the nature of drug, commercial, or lab scale.[14,15] The applications of liposomes in herbal formulations have been investigated widely and its evident from latest researches that are more focused on enhancing the bioavailability of phytoconstituents.[13,16] The potential applications of liposomes in phytoconstituents are given in Table 2.

POLYMERIC NANOPARTICLES

The versatility in nanotechnology provides an emerging drug delivery system for targeting the drugs at the desired

Table 1: Advantages and disadvantages of CRDDS

Advantages	Disadvantages
Eliminates peak-valley fluctuations	Fluctuations in peak and valley plasma concentration
Reduction in dosing frequency leads to poor patient compliance	Increasing dosing frequency leads to improved patient compliance
Reduction in GI irritation and other dose-related side effects	Due to the first pass metabolism in liver, GI irritation is more pronounced
Provides sustained release for longer period of time	High cost of formulation
Avoidance of night time dosing	Dose dumping

GI: Gastrointestinal

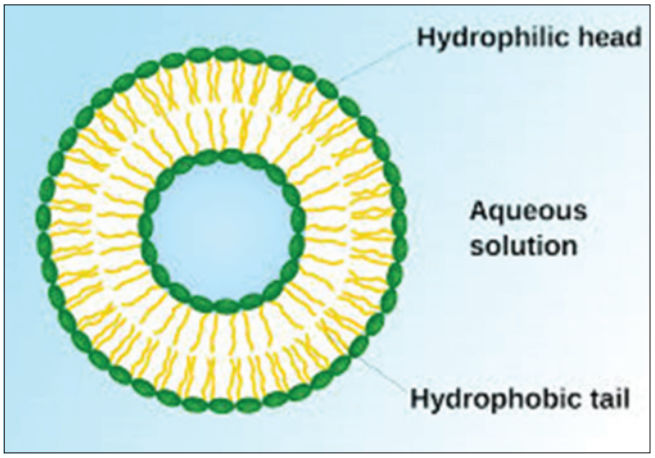

Figure 3: Basic cross section of liposome (Reproduced from Ref. 14)

site. Nanoparticles are colloidal particles having submicron size ranges from 10 to 1000 nm. Nanospheres contain a matrix structure in which active pharmaceutical ingredient is entrapped. Nanocapsules contain a membrane made up from polymers in which the API is present in the core of the polymer. Nanoparticles are effective systems for encapsulating a wide variety of drugs from small molecular weight compounds to larger molecules. In recent times, nanoparticles are more focused on herbal drug formulations. The drug release from nanoparticles is either through by bulk erosion in the matrix or by surface erosion in the polymer depend on the nature of drug and method of preparation adopted [Figure 4].[28-31]

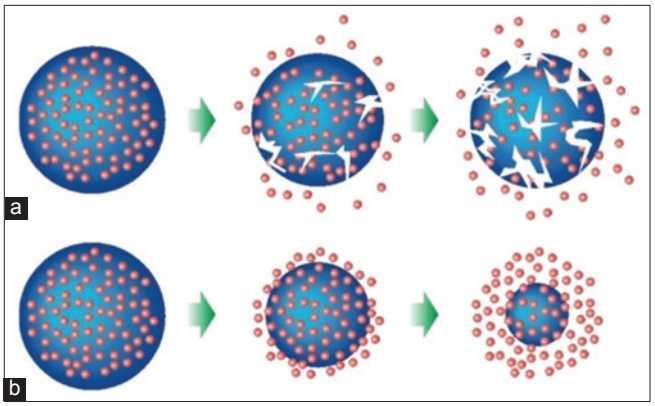

Figure 4: Mechanism of drug release (a) Bulk erosion (b) Surface erosion (Reproduced from ref.30)

There are various methods used for the preparation of nanoparticles, including salting out method, solvent

Table 2: Studies reporting enhanced bioavailability after incorporation into liposomes

Phytoconstituent	Chemical nature and source	Pharmacological activity	Method of delivering	Clinical significance	References
Camptothecin	Quinoline alkaloid, obtained from *Camptotheca acuminate*	Useful in ovarian, bladder, colon, and lung cancer	Multilamellar vesicles given orally	Reduction in adverse effects due to improved targeting	17
Quercetin	Pentahydroxyflavone, obtained from *Sophora japonica* L.	Antioxidant and antineoplastic	Elastic liposomes	Encapsulation efficiency was increased by 97%	18
Curcumin	Diarylheptanoid, obtained from *Curcuma longa*	Anticancer, anti-inflammatory, wound healing properties	Transdermal delivery of liposomes	Improved bioavailability and clinical efficacy	19
Vincristine	Bisindole alkaloid, obtained from *Catharanthus roseus*	Broad spectrum anticancer activity against lung and prostate cancer	Intravenous liposome delivery	Overcome Neurotoxicity problems and other side effects	20
Catechins	Polyphenolic compounds, obtained from *Camellia sinesis*	Antioxidant, antiobesity, anti-inflammatory, antidiabetic	Transdermal liposomes	Enhanced bioavailability five-fold higher	21
Silymarin	Flavonoid, obtained from milk thistle plant *Silymarin marianum*	Hepatoprotective	Buccal liposomal delivery	Enhanced bioavailability and clinical efficacy 2-fold higher	22,23
Breviscapine	Biphenolic compound, obtained from *Scutellaria barbata*	Antitumor activity against ovary and breast cancer cells	Injectable multilamellar liposomes	Improved systemic circulation and MRT	24
Paclitaxel	Taxol nucleus, obtained from *Taxus bacatta* and *Taxus bevifolia*	Broad anticancer activity against almost all types of cancer	Injectable liposomal delivery	Improved antitumor activity by selective targeting in cancerous cells	25
Colchicine	Benzofuran compound, obtained from *Colchicum autumnale*	Anti-gout	Delivering liposome through film dispersion	Optimum encapsulation efficiency and stability	26
Ampelopsin	Dihydromyricetin, a flavonol obtained from *Cercidiphyllum japonicum*	Antipyretic, useful in liver disorders	Oral delivery by Film ultrasound method	Entrapment ratio is higher, and leakage rate is low in liposomal formulations	27

MRT: Mean residence time

evaporation method, nanoprecipitation, and dialysis method, are widely used for lab scale as well as commercial purposes.[31,32] The applications of polymeric nanoparticles in herbal technology have a wide scope and are widely focused.[33-35] Studies show clinical significance upon incorporation of herbal drugs into nanoparticles are explained in Table 3.

EMULSION BASED FORMULATIONS

Emulsions are thermodynamically unstable formulations of oil and water phase, stabilized by a suitable emulsifying agent. Microemulsions are thermodynamically stable and are isotropic mixtures of oil, water, and surfactant with a droplet size of 100-200 nm [Figure 5). Microemulsion is widely used drug delivery formulations to improve the solubility of poorly soluble drugs. Microemulsions possess various advantages such as good thermodynamic stability, ease of manufacturing, fewer chances of drug degradation, and improved stability.[46,47]

The scope of microemulsions in herbal drug delivery is wide and has used clinically as well as commercially.[49,50] Curcumin has a wide biological activity like anti-inflammatory, anticancer but have no use clinically because of his poor solubility (1.0 ug/ml) and poor bioavailability (10%), the microemulsion formulation of curcumin has better stability, enhanced drug release up to 97%, and enhanced Cmax leads to enhanced biological activity.[51] Studies reporting enhanced bioavailability upon incorporation into microemulsion are given in Table 4.

PHYTOSOMES

The term phytosome is derived from two words, "Phyto" means plant and Some" means cell. Phytosome is a patented technology developed by a leading industrialist in phytopharmaceuticals to produce lipid drug molecular

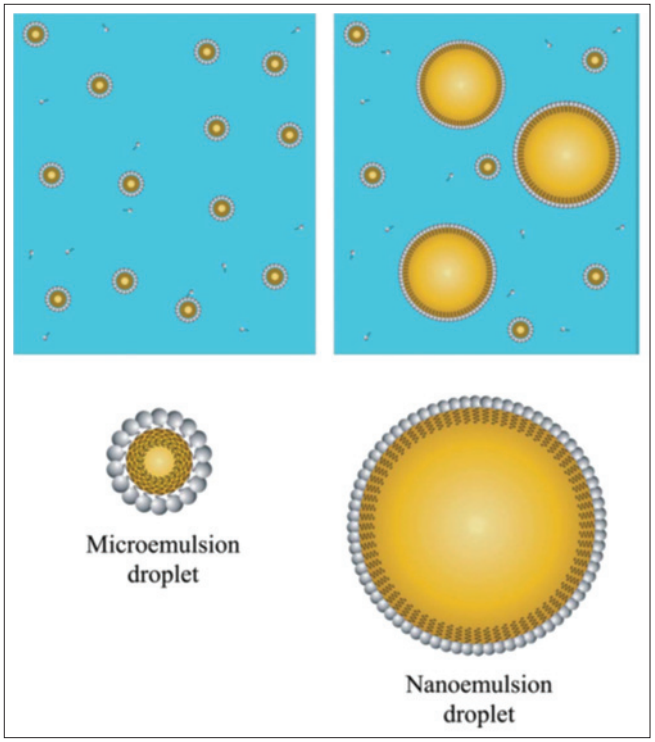

Figure 5: Illustration of differences in the size range between micro and nanoemulsion (Reproduced from Ref. 48)

Table 3: Studies reporting enhanced bioavailability after incorporation into polymeric nanoparticles

Phytoconstituent	Chemical nature and source	Pharmacological activity	Clinical significance upon incorporation	References
Hypericin	Napthodianthrone, obtained from *Hypericum perforatum*	Photosensitizer used in radiotherapy	Improved lipophilicity in physiologically active media and improved their diagnostic applications	36
Triptolide	Diterpenoid triepoxide, obtained from chinese herb, *Tripterygium wilfordii*	Useful in autoimmune disorders, antineoplastic	Improved aqueous solubility and reduced toxic effects due to enhanced targeting into the desired area	37
Berberine	Isoquinoline compound, obtained from *Berberis aquifolium*	Anticancer	Sustain the delivery of phytoconstituent lead to enhanced duration of action	38,39
Ginseng	Steroidal compound, obtained from *Panax ginseng, Panax quinquefolius*	Antioxidant activity	Enhanced stability, therapeutic action, and drug release	40
Tertandrine	Bis-isoquinoline alkaloid, obtained from *Stephania tetrandra*	Calcium channel blocker	Improved vasodilatory activity	41,42
Naringenin	Counmarin compound, obtained from	Immunomodulator	Improved drug loading and antioxidant activity	43,44
Glycyrrhizic acid	Steroidal saponin, obtained from *Glycyrrihiza glabra*	Antihypertensive, useful in hepatitis	Improved drug release and encapsulation efficiency	45

complexes. Phytosome contains herbal drug or phytoconstituent entrapped in an aqueous core surrounded by a lipid bilayer, consists of phosphotidylcholine. The phosphotidylcholine moiety has gastroprotective properties, protect the drug from the degradation by gastric enzymes and secretions. While comparing with a liposome, which is the composition of water-soluble substance with phospholipid in a definite proportion with no chemical bonds formed, the phytosome contain herbal drug with phosphotidylcholine in a different ratio depending on the molecule complexed with the formation of chemical bonds. Phytosome found superior to liposome in topical delivery and skin permeation enhancement. Phytosome has improved pharmacokinetic and pharmacodynamics parameter that used to enhance the bioavailability of many popular herbal extracts including milk thistle, grape seed, and gingko biloba. Phytosome is more bioavailable and enhanced solubilization capacity to cross the lipid bilayer membrane and then reaches the systemic circulation and provides therapeutic effect.[60-63]

Phytosome has wide research in phytoconstituents of biological origin, and few commercial products are available in the market [Figure 6] which the people take profit of it. Table 5 describes studies which enhance the bioavailability of phytoconstituents upon incorporation into phytosomes.[35,64,65]

MICROSPHERES

Microspheres are solid, almost spherical in nature, having a diameter in the range of 1 um-1000 um in which drug is dispersed in finely divided form or crystalline form. Microspheres are made up of various polymeric materials including natural polymers such as albumin, gelatin, and chitosan; or synthetic polymers including polylactic acid

Figure 6: Pictures of marketed formulations of phytosomes

Table 4: Studies reporting enhanced bioavailability upon incorporating herbal drug into microemulsions

Phytoconstituent	Chemical nature and source	Pharmacological activity	Clinical significance	References
Curcumin	Diarylheptanoid, obtained from *Curcuma longa*	Anticancer activity, anti-inflammatory activity	Improved permeation and enhancement ratio via transdermal delivery	52
Triptolide	Diterpenoid triepoxide, obtained from Chinese herb, *Tripterygium wilfordii*	Useful in autoimmune disorders, antineoplastic	Microemulsion based hydrogel provides improved percutaneous permeability and better-sustained release profile	53
Psoralen	Counmarin glycoside, obtained from *Psoralea corylifolia*	Useful in skin disorders, leprosy, and anti-inflammatory	Topical delivery via microemulsion provides better *in vivo* anti-inflammatory effect	54
Silybin	Flavolignans, obtained from *Silybum marianum*	Broad spectrum activity against human prostate adenocarcinoma cells	Microemulsion vehicle shows prolonged release profile as compared to silymarin solution	55
Docetaxel	Taxol comound, obtained from taxus species (*Taxus bacatta, Taxus brevifolia*)	Broad spectrum antimitotic compound against all types of cancer	Docetaxel microemulsion provides improved apical to basolateral transport across Caco-2 cells	56
Berberine	Pyrimidine compound, obtained from *Berberis aristata*	Antineoplastic in nature	Absorption rate high in the intestine and shows better drug release profile	57,58
Puerarin	Isoflavone compound, obtained from Radix puerariae	Useful in cardiovascular disorders	$AUC_{0-\infty}$ was 15.82-fold higher in microemulsion as compared to puerarin suspension	59

Table 5: Studies reporting enhanced bioavailability upon incorporating herbal drug into phytosomes

Phytoconstituent/ plant	Chemical nature and source	Pharmacological activity	Clinical significance	References
Ginkgo biloba	Kew tree or maiden hair tree, obtained as dried leaves belong to family Gingkoaceae	Cardioprotective, antioxidant	Increased antioxidant activity as compare to commercial formulation	66
Silybin	Flavolignan, obtained from the milk thistle plant (*Silybum marianum*)	Hepatoprotective	Improved mean residence time and AUC	67
Curcumin	Diarylheptanoid, obtained from *Curcuma longa*	Anti-inflammatory, anticancer	Chitosan microspheres provide improved drug targeting and bioavailability	68
Quercetin	Pentahydroxyflavone, obtained from *Sophora japonica* L.	Antineoplastic	Better encapsulation efficacy and drug release	69
Oxymatrine	Quinolizidine alkaloidal compound extracted from the root of *Sophora flavescens*	Antiviral	The drug - phospholipid complex will deliver at active site in desired concentration produces a better therapeutic effect	70
Embelin	Benzoquinone flavonoid, obtained from *Embelia ribes*	Antibacterial and antifertility activity	EPC showed 99.80% release as compare to conventional embelin solution	71
Marsupium	Marine compound, obtained from *Pterocarpus marsupium*	Antiviral	Phospholipids will prevent biological degradation of drug in the body and provide therapeutic effect	72
Epigallocatechins	Catechin nucleus, obtained from various species of Terminalia plant	Anticancer and antioxidant	Catechins in phytosomes have better antioxidant activity as compared to commercial formulation	73

and polyglycolic acid and waxes such as beeswax and carnauba wax. Microspheres are having wide commercial applications including sustained drug delivery, overcome handling issues with potent molecules and improved targeting at the active site in desired concentration to maintain overall effective plasma concentration for a longer period of time.[74,75]

The release mechanism of microsphere follows first order kinetics having dissolution and diffusion are two main mechanisms for drug release. The outer layer of polymer is first dissolved, and the dissolution media will diffuse the polymer matrix makes the entrapped drug to release in the matrix. The rate of drug release depends on the type of matrix used and drug/polymer concentration.[76]

Microspheres are widely used as drug delivery carrier for targeting of various agents that cause dose-dependent adverse effects. In recent times, microspheres are widely used to enhance the therapeutic potential of various poorly soluble phytoconstituets. Various techniques such as gastroretentive bloating microspheres, microencapsulation, emulsification, and calcium alginate based beads are used widely for herbal drug delivery. Table 6 shows the studies enhancing the therapeutic potential of phytoconstituents upon incorporation into microspheres.

TOPICAL DRUG DELIVERY APPROACHES

Delivery of phytoconstituents via skin is widely investigated for enhancing permeation and therapeutic efficacy. The topical delivery possesses major advantages such as avoidance of first pass metabolism, decrease adverse effects associated with oral and intravenous (IV) doses, effective maintenance of cars, and improved therapeutic efficacy. Various strategies are used to enhance the transdermal permeation including transdermal patches, ethosomes, transferosomes, and SLNs.[83-85]

Transdermal patches are the novel approach which utilizes permeation enhancers (Terpenes, ozones, and surfactants) for topical delivery. Various physical methods are used such as iontophoresis, sonophoresis, microneedles, and skin electroporation for delivery of the drug through a transdermal patch. The transdermal patch utilizing rate controlling membrane to sustain the delivery of the drug via the skin into the blood stream.[86,87] The main limitation in transdermal patch approach that it causes skin irritation or skin infection due to the high frequency applied through iontophoresis, which will overcome by the novel vesicular carriers such as transferosomes and ethosomes, which supplies essential nutrients results in maintain the integrity of the skin. Ethosomes are phospholipid based vesicles contains a high

Table 6: Studies reporting enhanced bioavailability upon incorporating herbal drug into microspheres

Phytoconstituent/ Plant name	Chemical nature and source	Pharmacological activity	Clinical significance	References
Rutin	Flavonoid glycoside, obtained from *Carpobrotus edulis*	Antioxidant	Microspheres shows sustained release behavior for the drug within 20 h, and still maintain existed within 180 h	77
Zedoary essential oil	Essential oil, obtained from *Curcuma zedoaria Roscoe*	Hepatoprotective	3-fold higher bioavailability as compare to conventional formulation	78
Camptothecin	Quinoline alkaloid, obtained from *Camptothecin acuminata*	Antineoplastic	CPT encapsulated in PLGA microspheres should retain its antitumor potency for longer period of time	79
Quercetin	Pentahydroxyflavone, obtained from *Sophora japonica* L.	Antioxidant and anti-inflammatory	Controlled drug delivery for effective management of arthritis	80
Ginsenosides	Steroidal glycoside, obtained from Panax species (*Panax ginseng, Panax notofolium*)	Anticancer, Immunomodulator	PLA microspheres shows improved drug release behavior and encapsulation efficiency	81
Silymarin	Flavolignan, obtained from milk thistle plant (*Silybum marinum*)	Hepatoprotective	Floating microspheres of silymarin exhibited prolonged drug release and excellent stability	82

CPT: Camptothecin, PLGA: Poly (D, L-Lactic-co-Glycolic Acid), PLA: Polylactide

Table 7: Studies reporting enhanced permeation and therapeutic efficacy upon incorporating herbal drug into various topical delivery strategies

Phytoconstituent/ plant	Pharmacological activity	Formulation strategy	Clinical significance	References
Khellin	Anti-acne, used in psoriasis	Transdermal patch using iontophoresis	Transdermal gel containing khellin was able to permeate more deeply and provide more effective treatment of psoriasis	93
Caffeine from the extract of *Paullinia cupana*	CNS stimulant	Transdermal patch	Transdermal patch was effective releasing all components simultaneously as compare to commercial formulation	94
Sophora alopecuroides	Anticancer and anti-inflammatory	Ethosomes	Ethosomes containing drug bypass the first pass metabolism and reaches drug more deeply into the skin for therapeutic effect	95
Matrine	Antibacterial	Ethosomes	Ethosomes containing matrine enhances the permeation and antibacterial effect	96
Curcumin	Anticancer, antioxidant and anti inflammatory	Transferosomes	Formulation shows higher entrapment efficiency and higher permeation of drug from transfersomal gel	97
Capsaicin	Analgesic and antirheumatic	Transferosomes	Better analgesic activity via topical delivery as compare to commercially available oral formulation	98
Vincristine	Antimitotic	Transferosomes	Compare to oral and IV formulation, the retention time of topical formulation in extended by 12 h	99
Triptolide	Used in auto-immune disease	SLNs	The anti-inflammatory activity is higher in SLN dispersion for rheumatoid arthritis	100,101

CNS: Central nervous system, IV: Intravenous, SLN: Solid lipid nanoparticles

content of ethanol (20-50%) which itself act as a permeation enhancer in transdermal delivery. Compare to other carriers, ethosomes have the capability to permeate the drug more deeply and more efficiently into the systemic circulation.[88,89]

On the other hand, transferosomes are also used as potential carriers for topical delivery. Transferosomes utilizing the osmotic pressure and hydration to increase permeation. These two vesicular carriers are widely used in topical drug

delivery to enhance the permeation and therapeutic efficacy of phytoconstituents.[90]

SLNs are widely used drug delivery carriers for topical application. SLN comprises lipid excipients which become solid at room temperature. SLN has a mean diameter of colloidal nature ranges from 50-1000um. The advantages of SLNs, including potential targeting at the active site in desired concentration, prevent degradation of drugs, improved drug loading and encapsulation efficiency, and reduction of drug toxicity. Various methods are used for the preparation of SLNs including homogenization, microemulsion, ultrasonification, and solvent diffusion method.[91,92] These topical approaches would prove as an effective drug delivery of phytoconstituents as compared to oral and IV. Table 7 shows various studies which increase permeation of phytoconstituents through topical drug delivery strategies.

CONTROLLED RELEASE DEVICES

Various approaches are used to enhance the therapeutic efficacy of phytoconstituents by formulating into controlled release drug delivery system. The versatility of this system

Table 8: Recent patients on novel drug delivery system of phytoconstituents

Patient number	Inventor	Publishing date	Description	References
US 20140141108 A1	Kenneth Brown, Brandi M Scott	2014-05-22	This present invention relates to an herbal composition (red quebracho extract) that treats various diseases, including bloating, constipation and there of	107
US 20070042062 A1	Palpu Pushpangadan, Chandana Rao, Ajay Rawat, Dadala Kumar	2007-02-27	This present invention relates to novel herbal formulation contain *Curcuma longa* and *Zingiber officinale* Linn. rhizomes extract for the treatment of diabetes mellitus	108
US 7968115 B2	Razelle Kurzrock, Lan Li, Kapil Mehta, Bharat Bhushan Agarawal	2011-06-28	This present invention relates to the novel liposomal formulation of curcumin for the treatment of pancreatic, breast, and melanoma cancer	109
US 6312736 B1	Gregory J. Kelly, Ann Perry	2001-11-06	This present investigation deals with various extracts such as white willow bark extract, kava kava root extract, feverfew extract, ginger root extract, Guarana extract for the relief of pain and its associated conditions	110
US 20100104646 A1	Ji Hwal Kim	2010-04-29	This present invention deals with nanoparticle composition comprises mixture of *Zanthoxylum piperitum, Cnidium officinale* encapsulated It using lecithin and chitosan to produce lecithin-capsuled nanoparticles	111
EP 2437725 A1	Manu Chaudhary, Vijay Naithani	2012-04-11	This present invention deals with topical microemulsion composition comprises various ratio of oil, water, and surfactant and herbal phytoconstituent includes *Piper nigrum, Zingiber officinale, Piper longum, Cinnamomum zeylanicum, Cinnamomum tamala, Vitex negundo, Boswellia* serrate that will used for the treatment of rheumatoid arthritis	112
US 6703034 B2	Balraj S. Parmar, Manoj Varshney, Dinesh O. Shah	2004-03-09	This present invention deals with the microemulsion composition of neem oil contain oil, non-ionic surfactant, and water for the treatment of various diseases	113
US 20050042271A1	Weihong Xiong, Dinesh Patel	2005-02-24	This present investigation deals with alkaloids of *Aconitum* species incorporated in a transdermal drug delivery system for the treatment of pain and inflammation	114
WO 2005034923 A1	Dominique Marechal, Wel-Hong Yang, Yu-Zhang Hu	2005-04-21	This invention deals with the formulation of sustained release granules of gingko biloba extract as well as the process for preparing it	115

is explained by first marketed controlled release product known as ocusert®. Ocusert is a controlled release product used for topical delivery of eye for the treatment of open eye glaucoma. Ocusert contains pilocarpine as an active pharmaceutical ingredient, aparasympathomimetic alkaloid obtained from various species of pilocarpus, mostly from *Pilocarpus Jaborandi* and *Pilocarpus Microphyllus*. This device will provide sustained drug delivery for a longer period of time.[102]

Another approach of controlled drug delivery is by formulating into polymeric implants. Implants are polymeric devices which provide controlled drug delivery of wide variety of drugs. However, its scope is wide in enhancing the therapeutic efficacy of phytoconstituents in a sustained manner.[103] Danshen is an active phytoconstituent obtained from *Radix Salviae Miltiorrhizae*, is formulated into implant contain chitosan and gelatin as a natural polymer enhances the therapeutic efficacy of healing muscles and tissues in the abdominal cavities.[104]

Micropellets are also the widely used controlled release device for sustained drug delivery. It is made up of solid particles in the range of 1-1000 um. Micropellets are widely used for taste masking, enteric coating, and preventing drug degradation from biological environment. It also used for delivery of two incompatible drugs simultaneously at same or different sites.[105] Curcumin were formulated into Pectin-hydroxypropyl methylcellulose coated pellets which provide sustained drug delivery and gives better results for inflammatory disease [Table 8].[106]

REFERENCES

1. Jing J, Sklar EG, Vernon SO, Cheun S. Factors affecting therapeutic compliance: A review from the patient"s perspective. Ther Clin Risk Manag 2008;4:269-86.
2. Solecki RS, Shanidar IV. A neanderrhal flower burial in northen Iraq. Science 1975;190:880-1.
3. Salanki A, Kutty SK. Plant derived compounds in clinical trials. Drug Discov Today 2007;13:161-71.
4. Available from: http://www.apps.who.int/medicinedocs/en/d/Js7916e/7.12.html. [Last Accessed on 2015 Dec 14].
5. Park K. Controlled drug delivery systems: Past forward and future back. J Control Release 2014;190:3-8.
6. Hoffman AS. The origin and evolution of controlled drug delivery systems. J Control Release 2008;132:153-63.
7. Srikanth P, Raju N, Raju WS, Raj B. A review on oral controlled drug delivery. Int J Adv Pharm 2013;3:51-8.
8. Huang X, Brazel CS. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J Control Release 2001;73:121-36.
9. Jha SK, Dey S, Karki R. Microemulsions-potential carrier for improved drug delivery. Asian J Biomed Pharm Sci 2011;1:5-9.
10. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. Int J Pharm 2003;255:13-32.
11. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. Eur J Pharm Biopharm 2000;50:161-77.
12. Brannon-Peppas L. Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery. Int J Pharm 1995;116:1-9.
13. Musthaba SM, Baboota S, Ahmed S, Ahuja A, Ali J. Status of novel drug delivery technology for phytotherapeutics. Expert Opin Drug Deliv 2009;6:625-37.
14. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev 2013;65:36-48.
15. Xu X, Burgess DJ. Liposomes as carriers for controlled drug delivery. Adv Deliv Sci Technol 2011;3:195-220.
16. Ajazuddin, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia 2010;81:680-9.
17. Flaten GE, Chang TT, Phillips WT, Brandl M, Bao A, Goins B. Liposomal formulations of poorly soluble camptothecin: drug retention and biodistribution. J Liposome Res 2013;23:70-81.
18. Priprem A, Sutthiparinyanont S, Young JS, Chulasiri M. Effect of formulations of nanosized quercetin liposomes on COX-2 and NF-kB in MCF-10A cells. Pharm Nanotechnol 2015;1:26-34.
19. Li L, Braiteh FS, Kurzrock R. Liposome-encapsulated curcumin: *In vitro* and *in vivo* effects on proliferation, apoptosis, signaling, and angiogenesis. Cancer Res 2005;104:1322-31.
20. Zhigaltsev IV, Maurer N, Akhong QF, Leone R, Leng E, Wang J, *et al*. Liposome-encapsulated vincristine, vinblastine and vinorelbine: A comparative study of drug loading and retention. J Control Release 2005; 104:103-11.
21. Fang JY, Hwang TL, Huang YL, Fang CL. Enhancement of the transdermal delivery of catechins by liposomes incorporating anionic surfactants and ethanol. Int J Pharm 2006;310:131-8.
22. Elmowafy M, Viitala T, Ibrahim HM, Abu-Elyazid SK, Samy A, Kassem A, *et al*. Silymarin loaded liposomes for hepatic targeting: In vitro evaluation and HepG2 drug uptake. Eur J Pharm Sci 2013;50:161-71.
23. Samaligy MS, Afifi NN, Mahmoud EA. Increasing bioavailability of silymarin using a buccal liposomal delivery system: preparation and experimental design investigation. Int J Pharm 2006;308:140-8.
24. Zhong H, Deng Y, Wang X, Yang B. Multivesicular liposome formulation for the sustained delivery of breviscapine. Int J Pharm 2005;301:15-24.
25. Yang T, Cui FD, Choi MK, Lin H, Chung SJ, Shim CK, *et al.* Liposome formulation of paclitaxel with enhanced solubility and stability. Drug Deliv 2007;14:301-8.
26. Singh HP, Utreja P, Tiwary AK, Jain S. Elastic liposomal formulation for sustained delivery of colchicine: *in vitro* characterization and *in vivo* evaluation of anti-gout activity. AAPS J 2009;11:54-64.

27. He ZF, Liu DY, Zeng S, Ye JT. Study on preparation of ampelopsin liposomes. Zhongguo Zhong Yao Za Zhi 2008;33:27-30.
28. Rao JP, Geckeler KE. Polymer nanoparticles: Preparation techniques and size-control parameters. Progress Polym Sci 2011;36:887-913.
29. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids Surf B Biointerfaces 2010;75:1-18.
30. Leo E, Scatturin A, Vighi E, Dalpiaz A. Polymeric nanoparticles as drug controlled release systems: a new formulation strategy for drugs with small or large molecular weight. J Nanosci Nanotechnol 2006;6:3070-9.
31. Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC. Polymeric nanoparticles for drug delivery. Methods Mol Biol 2010;624:163-75.
32. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 2001;70:1-20.
33. Chaturvedi M, Kumar M, Sinhal A, Saifi A. Recent developments in novel drug delivery systems of herbal drugs. Int J Green Pharm 2011;5:87-94.
34. Ansari SH, Islam F, Sameen M. Influence of nanotechnology on herbal drugs: A review. J Adv Pharm Technol Res 2015;3:142-6.
35. Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. Pharmacogn Rev 2010;4:27-31.
36. Zeisser-Labouebe M, Lange N, Gurny R, Delie F. Hypericin-loaded nanoparticles for the photodynamic treatment of ovarian cancer. Int J Pharm 2006;326:174-81.
37. Liu MX, Dong J, Yang YJ, Yang XL, Xu HB. Preparation and toxicity of triptolide-loaded poly (D,L-lactic acid) nanoparticles. Yao Xue Xue Bao 2004;39:556-60.
38. Khemani M, Sharon M, Sharon M. Encapsulation of berberine in nano-sized PLGA synthesized by emulsification method. ISRN Nanotechnol 2012;34;12-21.
39. Chang CH, Huang WY, Lai CH, Hsu YM, Yao YH, Chen TY, *et al.* Development of novel nanoparticles shelled with heparin for berberine delivery to treat Helicobacter pylori. Acta Biomater 2011;7:593-603.
40. Leonard K, Ahmmad B, Okamura H, Kurawaki J. *In situ* green synthesis of biocompatible ginseng capped gold nanoparticles with remarkable stability. Colloids Surf B Biointerfaces 2011;82:391-6.
41. Li X, Lu X, Xu H, Zhu Z, Yin H, Qian X, *et al*. Paclitaxel/ tetrandrine coloaded nanoparticles effectively promote the apoptosis of gastric cancer cells based on oxidation therapy. Mol Pharm 2012;9:222-9.
42. Xu H, Hou Z, Zhang H, Kong H, Li X, Wang H, *et al*. An efficient Trojan delivery of tetrandrine by poly(N-vinylpyrrolidone)-block-poly(ε-caprolactone) (PVP-b-PCL) nanoparticles shows enhanced apoptotic induction of lung cancer cells and inhibition of its migration and invasion. Dove Press 2013;9:231-42.
43. Yen FL, Wu TH, Tzung L, Cham TY, Ching CL. Naringenin-loaded nanoparticles improve the physicochemical properties and the hepatoprotective effects of naringenin in orally-administered rats with CCl_4-induced acute liver failure. Pharm Res 2009;26:893-901.
44. Panneerselvam S, Kumpati P, Saraswathy DP. Formulation, characterization and pharmacokinetic evaluation of naringenin-loaded gastroretentive mucoadhesive polymeric nanosystem for oral drug delivery. J Drug Deliv Ther 2015;2:107-14.
45. Tian Q, Wang W, He XT, Zhu XC, Huang W, Zhang CN, *et al*. Glycyrrhetinic acid-modified nanoparticles for drug delivery: Preparation and characterization. Chin Sci Bull 2009;54:3121-6.
46. Kumar R, Kumar MS, Mahadevan N. Multiple emulsions: A review. Int J Adv Pharm Res 2012;2:9-19.
47. Mujaffar F, Singh UK, Chauhan L. Review of microemulsion as futuristic drug delivery. Int J Pharm Pharm Sci 2013;5:39-51.
48. McClements DJ. Nanoemulsions versus microemulsions: Terminology, differences, and similarities. Soft Matter 2012;8:1719-29.
49. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm Res 2004;21:201-30.
50. Wasan KM. Role of Lipid Excipients in Modifying Oral and Parentral Drug Delivery. New York: Wiley Interscience; 2007.
51. Hu L, Jia Y, Niu F, Jia Z, Yang X, Jiao K. Preparation and enhancement of oral bioavailability of curcumin using microemulsions vehicle. J Agric Food Chem 2012;60:7137-41.
52. Sintov AC. Transdermal delivery of curcumin via microemulsion. Int J Pharm 2015;481:97-103.
53. Chen L, Zhao X, Cai J, Guan Y, Wang S, Liu H, *et al*. Triptolide-loaded microemulsion-based hydrogels: physical properties and percutaneous permeability. Acta Pharm Sin B 2013;3:185-92.
54. Ali J, Akhtar N, Sultana Y, Baboota S, Ahuja A. Antipsoriatic microemulsion gel formulations for topical drug delivery of babchi oil (*Psoralea corylifolia*). Methods Find Exp Clin Pharmacol 2008;30:277-85.
55. Panapisal V, Charoensri S, Tantituvanont A. Formulation of microemulsion systems for dermal delivery of silymarin. AAPS PharmSciTech 2012;13:389-99.
56. Yin YM, Cui FD, Mu CF, Choi MK, Kim JS, Chung SJ, et al. Docetaxel microemulsion for enhanced oral bioavailability: Preparation and in vitro and in vivo evaluation. AAPS Pharm Sci Technol 2009;140:86-94.
57. Gui S, Wu L, Pan J, Wen Z, Kai W, Wang J. Study on preparation of berberine microemulsion and its absorption in intestine. Zhongguo Zhong Yao Za Zhi 2009;34:398-401.
58. Gui SY, Wu L, Peng DY, Liu QY, Yin BP, Shen JZ. Preparation and evaluation of a microemulsion for oral delivery of berberine. Pharmazie 2008;63:516-9.
59. Wu H, Lu C, Zhou A, Min Z, Zhang Y. Enhanced oral bioavailability of puerarin using microemulsion vehicle.

Drug Dev Ind Pharm 2009;35:138-44.
60. Jain N, Gupta BP, Thakur N, Jain R, Banweer J, Jain DK, *et al*. Phytosome: A novel drug delivery system for herbal medicine. Int J Pharm Sci Drug Res 2010;2:224-8.
61. Amin T, Bhat SV. A review on phytosome technology as a novel approach to improve the bioavailability of nutraceuticals. Int J Adv Res Technol 2012;1:1-14.
62. Patel D. A review of phytosomes, their characterization, advancement and potential for transdermal application. J Drug Deliv Ther 2013;3:147-52.
63. Awasthi R, Kulkarni GT, Pawar VK. Phytosomes: An approach to increase the bioavailability of plant extracts. Int J Pharm Pharm Sci 2011;3:1-3.
64. Verma H, Prasad SB, Singh HP. Herbal drug delivery system: A modern era prospective. Int J Curr Pharm Rev Res 2013;4:88-101.
65. Goyal A, Kumar S, Nagpal M, Singh I. Potential of novel drug delivery system for herbal drugs. Indian J Pharm Edu Res 2011;45:225-35.
66. Naik SR, Pilgaonkar VW, Panda VS. Evaluation of antioxidant activity of *Ginkgo biloba* phytosomes in rat brain. Phytother Res 2006;20:1013-6.
67. Loguercio C, Ferti D. Silybin and the liver: From basic research to clinical practice. World J Gastroenterol 2011;17:2288-301.
68. Zhang J, Tang Q, Xu X, Li N. Development and evaluation of a novel phytosome-loaded chitosan microsphere system for curcumin delivery. Int J Pharm 2013;448:168-74.
69. Rasaie S, Ghanbarzadeh S, Mohammadi M, Hamishehk M. Nano phytosomes of quercetin: A promising formulation for fortification of food products with antioxidants. Pharm Sci 2014;20:96-101.
70. Yue PF, Yuan HL, Li XY, Yang M, Zhu YF. Process optimization, characterization and evaluation in vivo of oxymatrine–phospholipid complex. Int J Pharm 2010;387:139-46.
71. Pathan R, Bhandari U. Preparation and characterization of embelin-phospholipid complex as effective drug delivery tool. J Incl Phenom Macrocycl Chem 2010;22:121-8.
72. Sikarwar MS, Sharma S, Jain AK, Parial SD. Preparation, characterization and evaluation of Marsupsin-phospholipid complex. AAPS PharmSciTech 2008;9:129-37.
73. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev 2009;14:226-46.
74. Varde NK, Pack DW. Microspheres for controlled release drug delivery. Expert Opin Biol Ther 2004;4:35-51.
75. Freiberg S, Zhu XX. Polymer microspheres for controlled drug release. Int J Pharm 2004;282:1-18.
76. Alagusundaram M, Chetty SM, Umashankari K. Microspheres as a novel drug delivery sysytem - A review. Int J Chem Technol Res 2009;1:526-34.
77. Jiang HL, Cui YL, Qi Y. Microencapsulation of rutin in chitosan-coated alginate microspheres through internal gelation technique.Adv Mater Res 2013;716:433-58.
78. You J, Cui FD, Han X, Wang YS, Yang L, Yu YW. Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil. Colloids Surf B Biointerfaces 2006;48:35-41.
79. Tong W, Wang L, D'Souza MJ. Evaluation of PLGA microspheres as delivery system for antitumor agent-camptothecin. Drug Dev Ind Pharm 2003;29:745-56.
80. Natarajan V, Krithica N, Madhan B, Sehgal PK. Formulation and evaluation of quercetin polycaprolactone microspheres for the treatment of rheumatoid arthritis. J Pharm Sci 2011;100:195-205.
81. Zhang D, Guan LI, Jiang D, Chen X. Preparation and characterization of biodegradable polylactide (PLA) microspheres encapsulating ginsenoside Rg3. Chem Res Chin Univ 2008;24:588-91.
82. Garg R, Gupta GD. Gastroretentive floating microspheres of silymarin: Preparation and *in vitro* evaluation. Trop J Pharm Res 2009;9:59-66.
83. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol 2008;26:1261-8.
84. Benson HE, Watkinson AC. Topical and Transdermal Drug Delivery: Principles and Practice. New Jersey: Wiley Online Library; 2011.
85. Prausnitz MR, Langer R, Mitragotri S. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov 2004;3:115-24.
86. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol 2015;172:2179-209.
87. Dhiman S, Thakur GS, Rehni AK, Transdermal patches: A recent approch to new drug delivery system. Int J Pharm Pharm Sci 2011;3:26-34.
88. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. J Adv Pharm Technol Res 2010;1:274-82.
89. Akiladevi D, Sachinandan D. Ethosomes: A noninvasive approach for transdermal drug delivery. Int J Curr Pharm Res 2010;2:1-4.
90. Modi CD, Bharadia PD. Transfersomes: New dominants for transdermal drug delivery. Am J Pharm Technol Res 2012;2:71-91.
91. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian J Pharm Sci 2009;71:349-58.
92. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomed 2007;2:289-300.
93. Marconi B, Mancini F, Colombo P, Allegra F, Giordano F, Gazzaniga A, *et al*. Distribution of khellin in excised human skin following iontophoresis and passive dermal transport. J Control Release 1999;60:261-8.
94. Heard CM, Johnson S, Mossb G, Thomasa CP. *In vitro* transdermal delivery of caffeine, theobromine,

theophylline and catechin from extract of Guarana, *Paullinia cupana*. Int J Pharm 2006;317:26-31.
95. Zhou Y, Wei Y, Liu H, Zhang G, Wu X. Preparation and *in vitro* evaluation of ethosomal total alkaloids of Sophora alopecuroides loaded by a transmembrane pH-gradient method. AAPS PharmSciTech 2010;11:1350-8.
96. Zhaowu Z, Xiaoli W, Yangde Z, Nianfeng L. Preparation of matrine ethosome, its percutaneous permeation *in vitro* and anti-inflammatory activity *in vivo* in rats. J Liposome Res 2009;19:155-62.
97. Patel R, Singh SK, Singh S, Sheth NR, Gendle R. Development and characterization of curcumin loaded transferosomes for transdermal delivery. J Pharm Sci 2009;1:71-80.
98. Xiao-Ying L, Luo JB, Yan ZH, Rong HS, Huang WM. Preparation and *in vitro* and *in vivo* evaluations of topically applied capsaicin transfersomes. Yao Xue Xue Bao 2006;41:461-6.
99. Lu Y, Hou SX, Zhang LK, Li Y, He JY, Guo DD. Transdermal and lymph targeting transfersomes of vincristine. Yao Xue Xue Bao 2007;42:1097-101.
100. Mei Z, Chen H, Weng T, Yang Y, Yang X. Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. Eur J Pharm Biopharm 2003;56:189-96.
101. Mei Z, Li X, Wu Q, Hu S, Yang X. The research on the anti-inflammatory activity and hepatotoxicity of triptolide-loaded solid lipid nanoparticle. Pharmacol Res 2005;51:345-51.
102. Pollack IP, Quigley HA, Harbin TS. The ocusert pilocarpine system: Advantages and disadvantages. S Med J 1976;86:1296-8.
103. Saltzman WM, Fung LK. Polymeric implants for cancer chemotherapy. Adv Drug Deliv Rev 1997;26:209-30.
104. Zhao HR, Wang K, Zhao Y, Pan LQ. Novel sustained release implant of herbal extract using chitosan. Biomaterials 2002;23:4459-62.
105. Pollinger N. Microparticulates as drug carriers as pediatric use. Int J Pharm 2013;30:351-3.
106. Kumar RS, Kumar M, Ganesh GN. Formulation and evaluation of Pectin-HPMC coated curcumin pellets for colon delivery. Asian J Pharm 2009;3:138-42.
107. Brown K, Scott BM. Herbal supplements and methods of use thereof. US Patent (US 20140141108 A1), 2014.
108. Pushpangadan P, Rao C, Rawat A, Kumar D. Novel anti-diabetic herbal formulation. US Patent (US 20070042062 A1), 2007.
109. Kurzrock R, Li L, Mehta K, Aggarawal BB. Liposomal formulation of curcumin for the treatment of cancer US patent (US 20070042062 A1), 2011.
110. Kelly GJ, Perry A. Herbal composition to relieve pain. US Patent (US 6312736 B1), 2001.
111. Kim JH. Nanoparticle composition for prevention of hair loss and promotion of hair growth. US patent (US 20100104646 A1), 2010.
112. Chaudhary M, Naithani V. Topical micro-emulsions for the treatment of rheumatic disorders. US Patent (EP 2437725 A1), 2012.
113. Parmar BS, Varshney M, Shah DO. Neem oil microemulsion without cosurfactants or alcohols and a process to form the same. US Patent (US 6703034 B2), 2014.
114. Xiong W, Patel D. Transdermal delivery system for alkaloids of aconitum species. US Patent (WO 2005034923 A1), 2004.
115. Marechal D, Yang WH, Hu YZ. Sustained-releasemicrogranules containing gingko biloba extract and the process for manufacturing these. US Patent (US 20050042271A1), 2005.