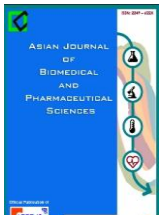
Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X



REVIEW ARTICLE

literati Open Access
rapid dissimination of knowledge

Received on: 01-09-2013
Accepted on: 20-09-2013
Published on: 15-10-2013

Raj Kumar Thapa *
School of Health and Allied Sciences, Pokhara University, Lekhnath-12, Dhungepatan, Kaski, NEPAL
Email: thapa.rajkumar7@gmail.com

QR Code for Mobile users

Conflict of Interest: None Declared !

Herbal Medicine Incorporated Nanoparticles: Advancements in Herbal Treatment

Raj Kumar Thapa*, Gulam Muhammad Khan, Kalpana Parajuli-Baral, Parbati Thapa.
School of Health and Allied Sciences, Pokhara University, Lekhnath-12, Dhungepatan, Kaski, NEPAL

Abstract

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

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

Cite this article as:
Raj Kumar Thapa, Gulam Muhammad Khan, Kalpana Parajuli-Baral, Parbati Thapa. Herbal Medicine Incorporated Nanoparticles: Advancements in Herbal Treatment. Asian Journal of Biomedical and Pharmaceutical Sciences 03 (24); 2013; 7-14 (review).

1. Introduction

Herbal remedies have been in practice since thousands of years and are a part of culture in countries like China, India and even Nepal. In recent decades the use of herbal drugs has significantly increased which is evident from the increased global market of herbal medicines.[1] Since herbal medicines have fewer side effects as compared to synthetic ones, their use has been increasing. Additionally, development of herbal dietary supplements and nutraceuticals have led to an increase in herbal market share.[2,3] However, the use of novel drug delivery systems for the formulation of herbal medicines is slow when compared to the complexity of the active constituents. Although several formulations for herbal drugs have been developed and they have demonstrated efficacy similar to that of chemically synthesized modern drugs, a lot more investigation is still warranted.

Among the novel drug delivery systems, nanoparticles are considered to be an important one. Nanoparticle can be used to target the herbal medicine to individual organ which improves the selectivity, drug delivery, effectiveness and safety and thereby reduces dose and increases patient compliance. The requirement of an ideal nanoparticulate system is that it should be capable of circulating in blood stream and should be small enough to reach target cells and tissues. Herbal medicines can be targeted to various organs such as brain, lung, liver, kidney, gastrointestinal tract, etc.[4,5]

The overall activity of herbal medicines depend on the active constituents present in them since they provide synergistic action and thus enhance the therapeutic value.[6,7] Most of the herbal actives are poorly water soluble because of their hydrophobic nature. This property leads to decreased bioavailability and increased systemic clearance thus necessitating repeated administration or increased dose, and thus limits the clinical use of herbal medicines. Therefore, nanoparticles can be utilized to increase the herbal drug solubility and help to localize the drug in a specific site thus resulting in better efficacy and improved patient compliance.

Development of different herbal medicine incorporated nanoparticle formulations

Different nanoparticle formulations have been developed to deliver herbal formulations. They are described below:

Polymeric nanoparticles:

Nanoparticles refer to colloidal systems with particle size ranging from 10 to 1000 nm. Nanoparticles have several advantages including solubility enhancement, bioavailability enhancement, efficacy enhancement, dose reduction and improved absorption of herbal medicines compared to traditional herbal dosage forms.[8-10]

Liu et al.[11] developed triptolide-loaded poly (DL-lactic acid) nanoparticles. To overcome the problems of poor solubility and toxicity of triptolide, nanoparticles were developed with biocompatible and biodegradable polymers, poly (DL-lactic acid).They were uniform in size, spherical in shape with smooth surface.

Sahu et al.[12] synthesized a new biodegradable and self-assembling polymer, methoxy poly (ethylene glycol)-palmitate, for curcumin delivery to cancer cells. The system comprised of methoxy poly (ethylene glycol) as hydrophilic part, palmitic acid as hydrophobic part and curcumin was present in the core of polymer micelle. The prepared micellar nanocarriers were spherical in shape.

For the prevention of the hydrolysis of camptothecin in physiological condition, Min et al.[13] developed hydrophobically modified glycol chitosan nanoparticles-encapsulated camptothecin for tumor targeting and better stability. The hydrophobic 5β-cholanic acid moiety was chemically conjugated with hydrophilic glycol chitosan backbone and camptothecin was encapsulated for intravenous administration.

Hypericin is a highly lipophilic agent and hence insoluble in physiologically acceptable media which makes its systemic administration problematic and restricts its diagnostic applications. To overcome these problems, an injectable suspension of polymeric nanoparticles with 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.[14]

Yang et al.[15] developed nanoparticles of *Cuscuta chinensis* by nanosuspension method to improve absorption of poorly water soluble constituent, quercetin. Similarly, Zhang and Kosaraju[16] studied a biopolymeric delivery system for controlled release of catechin. The antioxidant activity of catechin is decreased dramatically when it is introduced in an alkaline environment. In order to protect catechin, chitosan encapsulated catechin particles were developed. Also, Bhatia et al.[17] developed chitosan nanoparticles for the extract of *Ziziphus mauritiana* and checked the effect on its immunomodulatory activity.

Further information about the use of polymeric nanoparticles in herbal medicine delivery is presented in Table 1.

Herbal medicine	Chemical classification	Pharmacological activity	Polymeric nanoparticle formulation	Particle size	Encapsulation efficiency	Benefit of formulation	References
Triptolide	Diterpenoid triepoxide obtained from traditional Chinese medicine *Tripterygium wilfondil Hook F*	Used in the treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia and antineoplastic activity[18-20]	Poly (DL-lactic acid) nanoparticles	149.7 nm	85.7%	Enhanced solubility of triptolide and reduced toxicity	11
Curcumin	Natural polyphenol isolated from the root of *Curcuma longa*	Antitumor, antioxidant, antiamylodin, antiplatelet aggregation and anti-inflammatory[21]	Methoxy poly(ethylene glycol)-palmitate nanocarrier	41.43 nm	100%	Enhanced solubility and bioavailability of curcumin	12
Camptothecin	Cytotoxic quinoline alkaloid isolated from bark and stem of the oriental tree *Camptotheca acuminate*	Used in the treatment of gastric, rectum, bladder, colon, lung, breast and ovarian cancers[13]	Glycol chitosan nanoparticle	280-330 nm	80%	Improved solubility and stability of camptothecin with sustained release	13
Hypericin	Anthracene glycoside occurring in *Hypericum perofratum*	Photosensitizer used in photochemotherapy[14]	Polylactic acid/polylactic-co-glycolic acid nanoparticles	200-300 nm	70%	Improved hypericin solubility	14
Cuscuta chinensis (Active constituents – flavonoids and lignans such as quercetin, kaempferol)	Obtained from Chinese herbal medicine *Cuscuta chinensis Lam*	Used as tonic for the liver and kidney. Used to improve sexual function, prevent senescence and regulate the immune system. Some studies showed anticancer, antiageing and immune-stimulatory effects[22-27]	Nanoparticles (nanosuspension)	267 nm	90%	Enhanced solubility	15
Catechins (Active constituents – (+)-catechin, (-)-epicatechin, (-)-epigallocatechin-3-gallate)	Polyphenolic plant metabolites abundant in teas derived from the tea plant *Camellia sinensis*	Chemopreventive, anticarcinogenic, antiviral, antioxidative, anti-obesity, anti-inflammatory, antidiabetic, antimutagenic, antiangiogenic, antibacterial, antiageing activities[16]	Chitosan nanoparticles	1.97-6.83 µm	27.9-40.12%	Increased stability of catechins	16
Plant extract of *Ziziphus mauritiana*	Plant extract of *Ziziphus mauritiana*	Immunomodulatory activity[17]	Chitosan nanoparticles	-	-	Enhanced immunomodulatory activity of extract	17

Table 1: Polymeric nanoparticle herbal formulations

Liposomes

Liposomes are nanoparticulate systems that have been developed since more than four decades for drug delivery to specific site in the body.[28] Some properties like amphiphilicity, biocompatibility and biodegradability of liposomes are important for delivery of herbal drugs. Further advantages include improvement of therapeutic efficacy and safety, increased bioavailability, sustained release and localized drug delivery.[29]

Sou et al.[30] developed a modified nano-lipid vehicle loaded with curcumin to deliver it into tissue macrophages through intravenous injection. Curcumin was encapsulated into a phospholipid vehicle comprising 1,2-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.

Fang et al.[31] studied liposomal formulation encapsulating tea catechins. Permeation studies showed appreciable permeation of (+)-catechin when encapsulated in liposomes formulated with anionic surfactant deoxycholic acid and dicetyl phosphate in the presence of 15% ethanol. Another study by Lee et al.[32] developed calcium pectinate gel beads entrapping catechin-loaded liposomes for oral sustained delivery. Also, Samaligy et al.[28] increased the bioavailability of silymarin using buccal liposomal delivery systems. The liposomal formulations are further presented in Table 2.

Herbal medicine	Chemical classification	Pharmacological activity	Encapsulation efficiency	Benefit of formulation	References
Curcumin	Natural polyphenol isolated from the root of *Curcuma longa*	Antitumor, antioxidant, antiamylodin, antiplatelet aggregation and anti-inflammatory[21]	-	Improved intravenous delivery of curcumin to tissue macrophages	30
Catechins (Active constituents – (+)-catechin, (-)-epicatechin, (-)-epigallocatechin-3-gallate)	Polyphenolic plant metabolites abundant in teas derived from the tea plant *Camellia sinensis*	Chemopreventive, anticarcinogenic, antiviral, antioxidative, anti-obesity, anti-inflammatory, antidiabetic, antimutagenic, antiangiogenic, antibacterial, antiageing activities[16]	-	Improved loading and in vivo deposition of catechins	31
			70%	Sustained oral delivery of catechins	32
Silymarin (Active constituents – silybin, taxifolin, isosilybin, silydianin, silychristin)	Flavonol glycoside obtained from dried fruits of *Silybus marianum*	Hepatoprotective agent[28]	70%	Improved permeation and stability of silymarin	28

Table 2: Liposome herbal formulations

Proliposomes

Although liposomes possess several advantages for drug delivery, they still have some disadvantages of physicochemical instability (aggregation, sedimentation, fusion, phospholipid hydrolysis, oxidation and sterilization in large scale production). In order to overcome these problems a novel method for liposome production has been reported, namely proliposomes.[33,34] Proliposomes are dry, free flowing particles that immediately form liposomal suspension in contact with water. Solid properties of liposomes help resolve the stability problems of liposomes.

Yan-yu et al.[35] conducted a study on oral bioavailability of silymarin encapsulated into proliposome. Silymarin proliposomes had > 90% encapsulation efficiency with particle size of 196.4 nm. The study indicated improved bioavailability of silymarin in proliposome form as compared with pure silymarin.

Solid lipid nanoparticles

Solid lipid nanoparticles are nanoparticles ranging from 50-1000nm that are made from lipids which remain in a solid state at room and body temperature. Lipids used include mono-, di-, or triglycerides, lipid acids, and glyceride mixtures or waxes that are stabilized by the biocompatible surfactants. There are several advantages of solid lipid nanoparticles which include controlled drug release and drug targeting, protection of drug from chemical degradation, reduction of drug toxicity, enhancement of bioavailability, biodegradation, good tolerability, ability to incorporate both hydrophilic and lipophilic drugs, no problem with respect to large scale production and sterilization. The formulations incorporating herbal drugs in solid lipid nanoparticles include mouthwashes (e.g. peppermint oil), gargles (e.g. thymol) and inhalations (e.g. eucalyptus oil).[36-38]

Mei et al.[39] prepared triptolide incorporated solid lipid nanoparticles and studied the anti-inflammatory activity and transdermal delivery capacity. The formulation consisted of 5% tristearin glyceride, 1.2% soybean lecithin and 3.6% polyethylene glycol (400) monostearate. In other study, Mei et al. tried to reduce the hepatotoxicity induced by triptolide and improved its anti-inflammatory activity by formulating triptolide-incorporated solid lipid nanoparticles.[40]

Chen et al.[41] prepared podophyllotaoxin-loaded solid lipid nanoparticles and used them to target epidermis for the treatment of genital warts. Tiyaboonchai et al.[37] studied the stability of curcuminoid (curcumin, demethoxycurcumin and bisdemethoxycurcumin)-loaded solid lipid nanoparticles in cream because curcuminoids degrade by acidic and alkaline hydrolysis, oxidation and photodegradation. In another study, Li et al.[38] developed traditional Chinese medicine tetrandrine incorporated solid lipid nanoparticles to enhance the solubility of lipophilic tetrandrine. Hu et al.[42] prepared crytotanshinone incorporated solid lipid nanoparticles for enhancement of bioavailability of cryptotanshinone. Another study by Shi et al.[43] prepared solid lipid nanoparticles loaded with frankincense and myrrh oil. Further explanation of the solid lipid nanoparticle formulations is presented in Table 3.

Herbal medicine	Chemical classification	Pharmacological activity	Particle size	Encapsulation efficiency	Benefit of formulation	References
Triptolide	Diterpenoid triepoxide obtained from traditional Chinese medicine *Tripterygium wilfondil Hook F*	Used in the treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia and antineoplastic activity[18-20]	<200 nm	-	Enhanced anti-inflammatory and transdermal delivery of triptolide	39
			-	-	Reduced hepatotoxicity of triptolide	40
Podophyllotoxin (Active constituent-podophyllin)	Podophyllotoxin is a compound of resin mixture known as podophyllin obtained from the dried roots of *Podophyllum peltatum*	Antivirus in the treatment of warts through topical application and anticancer activity[41]	73.4 nm	-	Reduction of adverse effects of podophyllotoxin	41
Curcuminoids	Natural polyphenol isolated from the root of *Curcuma longa*	Antitumor, antioxidant, antiamylodin, antiplatelet aggregation and anti-inflammatory[21]	447 nm	70%	Enhanced stability of curcuminoids	37
Tetrandrine	Bisbenzylisoquinoline alkaloid extracted from the roots of stephania tetrandria	Anti-inflammatory, antiplatelet aggregation, and free radical scavenging activity[38]	157.3 nm	90.59%	Enhanced solubility and encapsulation of tetrandrine	38
Cryptotanshinone	Cryptotanshinone is the major active ingredient from the roots of *Salvia miltiorrhiza Bunge*	Anti-inflammatory, cytotoxic, anti-bacterial, anti-parasitic, anti-angiogenic and anti-oxidative[44-48]	121.4-137.5 nmm	94.2-96.3%	Enhancement of bioavailability of cryptotanshinone	42

Table 3: Solid lipid nanoparticle herbal formulations

Microemulsion

Microemulsion is a system of oil, water and amphiphile that is optically isotropic and thermodynamically stable liquid solution.[52] Among the various drug delivery systems, microemulsion is considered an ideal alternative for oral delivery of poor water-soluble compounds.[53] They have several advantages including ease of preparation, low viscosity, thermodynamic stability, enhanced dissolution of lipophilic drugs and bioavailability improvement.[54,55] Furthermore they can be administered through different routes such as transdermal, parenteral, pulmonary and ocular.[56]

Ali et al.[57] developed a novel microemulsion-based gel formulation of babchi oil (*Psoralea coryfolia*). Similarly, Wang et al.[58] made an attempt to enhance anti-inflammatory activity of curcumin by formulating it into nanoemulsion. In order to reduce the toxicity of triptolide, Chen et al.[56] studied microemulsion systems for transdermal delivery. Microemulsion preparations are further presented in Table 4.

Herbal medicine	Chemical classification	Pharmacological activity	Particle size	Benefit of formulation	References
Furocoumarin Psoralen	Occurs naturally in the seeds of *Psoralea coryfolia*	Treatment of skin diseases characterized by hyperproliferation such as psoriasis[57]	-	Enhanced anti-inflammatory effects	57
Curcumin	Natural polyphenol isolated from the root of *Curcuma longa*	Antitumor, antioxidant, antiamylodin, antiplatelet aggregation and anti-inflammatory[21]	61.8-79.5 nm	Enhanced anti-inflammatory effects	58
Triptolide	Diterpenoid triepoxide obtained from traditional Chinese medicine *Tripterygium wilfondil Hook F*	Used in the treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia and antineoplastic activity[18-20]	71.1 nm	Reduction in toxicity of triptolide following transdermal delivery	56

Table 4: Microemulsion herbal formulations

Conclusion

Herbal drugs have been recently getting more attention because of their potential to treat almost all diseases. However, several problems such as poor solubility, poor bioavailability, low oral absorption, instability and unpredictable toxicity of herbal medicines limit their use. In order to overcome such problems, nanoparticles can play a vital role. Hence, different nanoparticles including polymeric nanoparticles, liposomes, proliposomes, solid lipid nanoparticles and microemulsions showcase potential utilization to deliver herbal medicines with better therapy.

References

1. Solecki RS. A Neanderthal flower burial in northern Iraq. Science 1975;190:880-881.
2. Cardellina JH. Challenges and opportunities confronting the botanical dietary supplement industry. J Nat Prod 2000;65:1073-1084.
3. Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, Brinker A, Moreno DA, Ripoll C, Yakoby N, O'Neal JM, Cornwell T, Pastor I, Fridlender B. Plant and human health in the twenty-first century. Trends Biotechnol 2002;20:522-531.
4. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science 2004;303:1818-1822.
5. Kostarelos K. Rational design and engineering of delivery systems for therapeutics: biomedical excercises in colloid and surface science. Adv Colloid Interface Sci 2003;106:147-168.
6. Lu C, Lu Y, Chen J, Zhang W, Wu W. Synchronized and sustained release of multiple components in silymarin from erodible glyceryl monostearate matrix system. Eur J Pharm Biopharm 2007;66:210-219.
7. Williamson EM. Synergy and other interactions in phytomedicines. Phytomedicine 2001;8:401-409.
8. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MN. Role of antioxidants in prophylaxis and therapy: a pharmaceutical prospective. J Control Release 2006;113:189-207.
9. Allemann E, Gurny R, Doelker E. Drug loaded nanoparticles: preparation methods and drug targeting issues. Eur J Pharm Biopharm 1999;39:173-91.
10. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Del Rev 2002;54:631-651.
11. Liu M, Dong J, Yang Y, Yang X, Xu H. Anti-inflammatory effects of triptolide loaded poly (d.l-lactic acid) nanoparticles on an adjuvant-induced arthritis in rats. J Ethnopharmacology 2005;97:219-225.
12. Sahu A, Bora U, Kasoju N, Goswami P. Synthesis of novel biodegradable and self-assembling methoxy poly (ethylene glycol)-palmitate nanocarrier for curcumin delivery to cancer cells. Acta Biomaterialia 2008;4:1752-1761.
13. Min KH, Park K, Kim YS, Bae SM, Lee S, Jo HG, Park RW, Kim IS, Jeong SY, Kim K, Kwon IC. Hydrophobically modified glycol chitosan nanoparticles-encapsulated camptothecin enhance the drug stability and tumor targeting in cancer therapy. J Control Release 2008;127:208-218.
14. Labouebe ZM, Lange N, Gurny R, Delie F. Hypericin-loaded nanoparticles for the photodynamic treatment of ovarian cancer. Int J Pharm 2006;326:174-181.
15. Yen FL, Wu TH, Lin LT, Cham TM, Lin CC. Nanoparticles formulation of *Cuscuta chinensis* prevents acetaminophen-induced hepatotoxicity in rats. Food Chem Toxicol 2008;46:1771-1777.
16. Zhang L, Kosaraju SL. Biopolymeric delivery system for controlled release of polyphenolic antioxidants. Eur Poly J 2007;4:32956-32966.
17. Bhatia A, Shard P, Chopra D, Mishra T. Chitosan nanoparticles as carrier of immunorestoratory plant extract: synthesis, characterization and immunorestoratory efficacy. Int J Drug Del 2011;3:381-385.
18. Hachida HLM, Enosawa S, Suzuki XKLS, Koyanagi H. Immunosuppressive effect of triptolide in vitro. Transplant Proc 1999;3:2056-2057.
19. Zheng YL, Lin JF, Lin CC, Xy Y. Anti-inflammatory effect of triptolide. Zhongguo Yaoli Xuebao 1994;15:540-543.
20. Gang YY, Zhang ZX. Progress in pharmacological study of *Tripterygium wilfordii* and its active compounds. J China Pharm Univ 1995;26:252-256.
21. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin. A short review. Life Sci 2006;78:2081-2087.
22. Yen FL, Wu TH, Lin LT, Lin CC. Hepatoprotective and antioxidant effects of *Cuscuta chinensis* against

acetaminophen induced hepatotoxicity in rats. J Ethnopharmacol 2007;111:123-128.
23. Nisa M, Akbar S, Tariq M, Hussain Z. Effect of *Cuscuta chinensis* water extract on 7,12-dimethylbenz [a] anthracene-induced skin papillomas and carcinomas in mice. J Ethnopharmacol 1986;18:21-31.
24. Umehara K, Nemoto K, Ohkubo T, Miyase T, Degawa M, Noguchi H. Isolation of a new 15-membered macrocyclic glycolipid lactone, Cuscutic Resinoside a from the seeds of *Cuscuta chinensis*: a stimulator of breast cancer cell proliferation. Plant Medica 2004;70:299-304.
25. Liu JH, Jiang B, Bao YM, An LJ. Effect of *Cuscuta chinensis* glycoside on the neuronal differentiation of rat pheochromocytoma PC12 cells. Int J Dev Neurosci 2003;21:277-281.
26. Zheng HZ, Dong ZH, She J. Modern study of traditional Chinese medicine, First edition. Beijing Xue Yuan Press, People's Republic of China, Beijing; 1998. p. 4110-4120.
27. Bao X, Wang Z, Fang J, Li X. Structural features of an immunostimulating and antioxidant acidic polysaccharide from the seeds of *Cuscuta chinensis*. Plant Med 2002;68:237-243.
28. 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;308:140-148.
29. Samaligy MS, Afifi NN, Mahmoud EA. Evaluation of hybrid liposomes-encapsulated silymarin regarding physical stability and in vivo performance. Int J Pharm 2006;319:121-129.
30. Sou K, Inenaga S, Takeoka S, Tsuchida E. Loading of curcumin into macrophages using lipid-based nanoparticles. Int J Pharm 2008;352:287-93.
31. Fang JY, Hwang TL, Huanga YL, Fang CL. Enhancement of the transdermal delivery of catechins by liposomes incorporating anionic surfactants and ethanol. Int J Pharm 2006;310:131-138.
32. Lee JS, Chungb D, Hee HG. Preparation and characterization of calcium pectinate gel beads entrapping catechin-loaded liposomes. Int J Biol Macromol 2008;42:178-184.
33. Payne NI, Timmis P, Ambrose CV, Warel MD. Proliposomes a novel solution to an old problem. J Pharm Sci 1986;42:178-184.
34. Mayer LD, Baly MB, Hope KJ, Cullis PR. Techniques for encapsulating bioactive agents into liposomes. Chem Phys Lipids 1986;40:333-345.
35. Yan-yu X, Yun-Mei S, Zhi-Peng C, I-Neng P. Preparation of silymarin proliposome: A new way to increase oral bioavailability of silymarin in beagle dogs. Int J Pharm 2006;319:162-168.
36. Wong HL, Bendayan R, Rauth AM, Li Y, Wu XY. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Adv Drug Deliv Rev 2007;491-504.
37. Tiyaboonchai W, Tungpradit W, Plianbangchang P. Formulation and characterization of curcuminoids loaded solid lipid nanoparticles. Int J Pharm 2007;337:299-306.
38. Li Y, Dong L, Jia A, Chang X, Xue H. Preparation and characterization of solid lipid nanoparticles loaded traditional Chinese medicine. Int J Biol Macromolecules 2006;38:296-299.
39. 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;56:189-196.
40. 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;51:345-351.
41. Chen H, Chang X, Du D, Liu W, Liu J, Weng T, Yang Y, Xu H, Yang X. Podophyllotoxin-loaded solid lipid nanoparticles for epidermal targeting. J Control Release 2006;110:296-306.
42. Hu LD, Xing Q, Meng J, Shang C. Preparation and enhanced bioavailability of cryptotanshinone-loaded solid lipid nanoparticles. AAPS PharmSciTech 2010;11(2):582-587.
43. Shi F, Zhao JH, Liu Y, Wang Z, Zhang YT, Feng NP. Preparation and characterization of solid lipid nanoparticles loaded with frankincense and myrrh oil. Int J Nanomed 2012;7:2033-2043.
44. Kang BY, Chung SW, Kim SH, Ryu SY, Kim TS. Inhibition of interleukin-12 and interferon- γ production in immune cells by tanshinones from *Salvia miltiorrhiza.* Immunopharmacol 2000;49:355-361.
45. Wang AM, Sha SH, Lesinak W, Schacht J. Tanshinone (*Salviae miltiorrhizae* extract) preparations attenuate aminoglycoside-induced free radical formation in vitro and ototoxicity in vivo. Antimicrob Agents Chemother 2003;47:1836-1841.
46. Hur JM, Shim JS, Jung HJ, Kwon HJ. Cryptotanshinone but not tanshinone IIA inhibits angiogenesis in vitro. Exp Mol Med 2005;37:133-137.
47. Jin DZ, Yin LL, Ji XQ, Zhu XZ. Cryptotanshinone inhibits cyclooxygenase-2 enzyme activity but not its expression. Eur J Pharmacol 2006;549:166-172.
48. Don MJ, Shen CC, Syu WJ, Ding YH, Sun CM. Cytotoxic and aromatic constituents from *Salvia miltiorrhiza*. Phytochem 2006;67:497-503.
49. Van Vuuren SF, Kamamtou GPP, Vilijeon AM. Volatile composition and antimicrobial activity of twenty commercial frankincense essential oil samples. S Afr J Bot 2010;76(4):686-91.
50. Tipton DA, Lyle B, Babich H, Dabbous MKH. In vitro cytotoxic and anti-inlfammatory effects of myrrh oil on human gingival fibroblasts and epithelial cells. Toxicol in Vitro 2003;17(3):301-310.
51. Ashry KM, El-Sayed YS, Khamiss RM, El-Ashmawy IM. Oxidative stress and immunotoxic effects of lead and their amelioration with myrrh (*Commiphora molmol*) emulsion. Food Chem Toxicol 2010;48(1):236-241.
52. Lawrencea MJ, Reesb GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Del Rev 2000;45:89-121.
53. Yin YM, Cui FD, Mu CF, Choi MK, Kim JS, Chung SJ, Shim CK, Kim DD. Docetaxel microemulsion for enhanced oral bioavailability: preparation and in vitro and in vivo evaluation. J Control Release 2009;140:86-94.
54. Zhang H, Cui Y, Zhu S, Feng F, Zheng X. Characterization and antimicrobial activity of a pharmaceutical microemulsion. Int J Pharm 2010;395:154-160.
55. Zoumpanioti M, Stamatis H, Xenakis A. Microemulsion-based organogels as matrices for lipase immobilization. Biotech Adv 2010;28:395-406.

56. Chen H, Chang X, Weng T, Zhao X, Gao Z, Yang Y, Xu H, Yang X. A study of microemulsion systems for transdermal delivery of triptolide. J Control Release 2004;98:427-436.
57. Ali J, Akhtar N, Sultana Y, Baboota S, Ahuja A. Antipsoriatic microemulsion gel formulations for topical delivery of babchi oil (*Psoralea coryfolia*). Methods Find Exp Clin Pharmacol 2008;30:1-9.
58. Wang X, Jiang Y, Wang YW, Huang MT, Ho CT, Huang Q. Enhancing anti-inflammation activity of curcumin through O/W nanoemulsions. Food Chem 2008;108:419-424.