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HERBAL NANOFORMULATIONS – A REVIEW

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ABSTRACT

Herbal drugs have been getting more attention among scientists for the development of novel dosage forms formulations. 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. 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 variety of novel herbal formulations like polymeric nanoparticles, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. The current review highlights the development of novel nanocarrier for plant active compounds, their method of preparation, type of active ingredients, and their biomedical applications.

INTRODUCTION

Herbal therapy is an ancient science of Indian system of medicine. 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. The use of herbal medicines has gained popularity throughout the world in recent times, these medicinal plants and their phytochemical constituents are thought to have potential applications in the management of a wide range of health conditions. Many whole herbal preparations, herbal extracts and isolated phytoconstituents have been subjected to pharmacological and clinical research, in which The *in vitro* demonstrated benefits of the phytochemical constituents do not always translate directly to *in vivo* and clinically demonstrated benefits. This has highlighted issues such as poor bioavailability, stability and distribution of herbal medicines when administered in traditional dosage forms and paved the way for research into the incorporation of herbal medicines into novel drug delivery system. The novel carriers should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity of herbal drug to the site of action [2]. Nanotechnology is one of the key novel drug

delivery methods under investigation, with nanoformulations thought to have a wide variety of benefits in comparison with conventional preparations of plant constituents, which include enhanced permeability, solubility, bioavailability, therapeutic activity, stability, improved distribution within tissues and sustained delivery's. There are three main reasons for the popularity of herbal medicines:

- ✓ There is a growing concern over the reliance and safety of drugs and surgery.
- ✓ Modern medicine is failing to effectively treat many of the most common health conditions.
- ✓ Many natural measures are being shown to produce better results than drugs or surgery without the side effects.

The therapeutic and phytochemical importance of herbal medicine has been built for the improvement of human health, but its broader application is restricted due to the low bioavailability, the problems come with poor lipid soluble compounds due to limited membrane permeability. Many herbal products demonstrated low therapeutic action due to their solubility problems which finally resulted in low bioavailability despite their extraordinary potential. The salient features of novel herbal drug delivery systems include:

- Improved stability
- Bioavailability enhancement
- Bio compatibility issues
- Site specific delivery
- Release profile
- Dose reduction
- Minimizing toxicities
- Avoids pre systemic metabolism
- Facilitating patient compliance.

Types of herbal formulations

Herbal formulations include nanoemulsions, liposomes, phytosomes, transferosomes, nanoparticles, ethosomes, microspheres and solid-lipid nanoparticles.

LIPOSOMES: Liposomes are concentric bi-layered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bi-layer mainly composed of natural or synthetic phospholipids. The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse (float) into their interior. These are biodegradable, colloidal and spherical vesicles of 0.05-5.0 μm diameter, composed of a lipid bilayer membrane entrapping an aqueous core. The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely pass around or float into their interior. They can carry one, several or multiple concentric membranes. Some properties like amphiphilicity, biocompatibility and biodegradability of liposomes are important for delivery of herbal drugs [3]. Liposomes usually formed from phospholipids, have been used to change the pharmacokinetics profile of, not only drugs, but herbs, vitamins and enzymes. Because of their unique properties liposomes are able to enhance the performance of products by increasing ingredient solubility, improving ingredient bioavailability, enhanced intracellular uptake and altered pharmacokinetics and bio-distribution [4]. As drug carrier systems for topical treatment, liposomes are reported to be superior over conventional topical preparations. Phospholipids, being the major component of liposomal systems, are easily integrated with the skin lipids and maintain the desired hydration conditions to improve drug penetration and localization in the skin layers. Recently, a new generation of liposomes called 'stealth liposomes' have been developed. Stealth liposomes have the ability to evade the interception by the immune systems, and therefore, have longer half-life. The structure of liposome is shown in Figure1.

Advantages of drug loading in liposomes

Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene [9]. Liposome formulation can produce sustained and controlled release of formulation and enhances the drug. There are many benefits of administrating drug into liposomes. Some of them are listed in Table 1.

ETHOSOMES: Ethosomes are customized lipid vesicular carrier system represent ethanol in relatively high concentration and are very

effectual in delivering drugs into and across the skin [6]. These "soft vesicles" are very efficient at transporting active substances through the stratum corneum into the deeper layers of the skin than conventional liposomes. Ethosomes can act as a carrier for large and diverse group of drugs with different physicochemical properties and found a number of applications in pharmaceutical, biotechnological and cosmetic fields. The structure of ethosomes is shown in Figure 2. Ethosomes are mainly used for the delivery of drugs through transdermal route. These vesicular systems have higher penetration rate through the skin as compared to liposomes. Various herbal ethosomal formulations are listed in Table 3. Various herbal Phytosomal formulations are listed in Table 4. Various herbal Transferosomes formulations are listed in Table 5. Various herbal emulsion formulations are listed in Table 6.

Advantages of ethosomes:

1. Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).
2. Ethosomes composition is safe and the components are approved for pharmaceutical and cosmetic use.
3. Low risk profile- the technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature.
4. High patient compliance- The ethosomal drug is administrated in semisolid form (gel or cream), producing high patient compliance.
5. Relatively simple to manufacture with no complicated technical investments required for production of ethosomes.
6. Ethosomal system is passive, non-invasive and is available for immediate commercialization.

Phytosomes: Hydrophilic phytoconstituents can be complexed with clinically useful nutrients such as phospholipids to convert them into lipid soluble complexes. Such complexes can be used to prepare liposome-like vesicles called as phytosomes. Phytosomes show improved pharmacokinetic and therapeutic profiles than conventional herbal extracts. Phytosomes are prepared by use of polyphenolic phytoconstituents with phosphatidylcholine in the ratio of 1:2 or 1:1. The structure of phytosome is shown in Figure 3. Various herbal solid –lipid nanoparticle formulations are listed in Table 7.

TRANSFEROSOMES

The name means “carrying body”, and is derived from the Latin word 'transferee', meaning ‘to carry across’, and the Greek word ‘soma’, for a ‘body’. A transferosome carrier is an artificial vesicle which resembles the natural cell vesicle. Transferosomes are a special type of liposomes, consisting of phosphatidylcholine and an edge activator. They are soft malleable vesicles tailored for enhanced delivery of active agents [7]. The surfactants work as “edge activators,” conferring ultra-deformability on the structure of transferosomes, which helps them to squeeze through pores in the stratum corneum. phospholipids acts as vesicle forming material, surfactants to provide flexibility, alcohol as solvent and buffering agent as Hydrating medium. The structure of transferosomes is shown in the Figure 4.

NANOEMULSIONS

Emulsion is a biphasic system in which one phase is intimately dispersed in the other phase in the form of minute droplets ranging in diameter from 0.1 µm to 100 µm. In emulsion, one phase is always water or aqueous phase, and the other phase is oily liquid, i.e., non-aqueous. Among them, the micro-emulsion is also called nanoemulsions [8]. Factors to be considered during preparation of nanoemulsions. Surfactants must be carefully chosen so that an ultra low interfacial tension (< 10-3 mN/m) can be attained at the oil / water interface which is a prime requirement to produce nanoemulsions. Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the micro droplets to be produced by an ultra low interfacial tension. The interface must be flexible or fluid enough to promote the formation of nanoemulsions. The structure of nanoemulsion is shown in Figure 5.

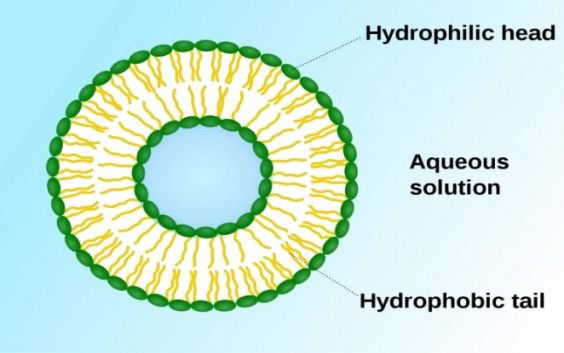

Figure 1. Structure of liposome

Table 1 Benefits of drug loading in liposomes

Benefits of drug loading	Examples
Improved solubility of lipophilic and amphiphilic drugs	Amphotericin B, porphyrins,minoxidil, some peptides, and Anthracyclines, respectively; hydrophilic drugs, such as anticancer agent doxorubicin or acyclovir.
Passive targeting to the cells of immune system, especially cells of mononuclear phagocytic system.	Antimonials, Amphotericin B, porphyrins, vaccines, immunomodulators.
Sustained release system of systemically or locally administrated liposomes	Doxorubicin, cytosine arabinoside, cortisones, biological proteins or peptides such as vasopressin.
Site specific targeting	Anti- inflammatory drug, anti cancer and anti-infection.
Improved transfer of hydrophilic charged molecules	Antibiotics, plasmids and genes.
Improved penetration into tissues	Corticosteroids, anesthetics and insulin.

Preparation methods of liposomes: Various herbal liposomal formulations are listed in Table 2.

Table 2. Examples of liposomal herbal formulations

Formulation	Active ingredient	Method of preparation	Route of administration	Biological activity	Applications
Curcumin liposome	Curcumin	Ethanol injection method	in vitro	Anti cancer	Long circulation and high entrapment efficiency.
Colchicine liposome	Colchicine	Rotary evaporation method	Topical	Anti gout	Enhance skin accumulation and prolong release.
Catechins liposomes	Catechins	Rotary evaporation method	Transdermal	Anti oxidant and chemo protective	Increase permeation through skin.
Breviscapine liposomes	Breviscapine	Double emulsification	Intramuscular	Cardiovasculars ystem diseases	Sustained delivery.
Ampelopsin liposome	Ampelopsin	Film- ultra sound method	*In vitro*	Anti cancer	Increases efficiency.
Wogonin liposome	Wogonin	Film dispersion method	*In vivo*	Anti cancer	Sustained release effect.

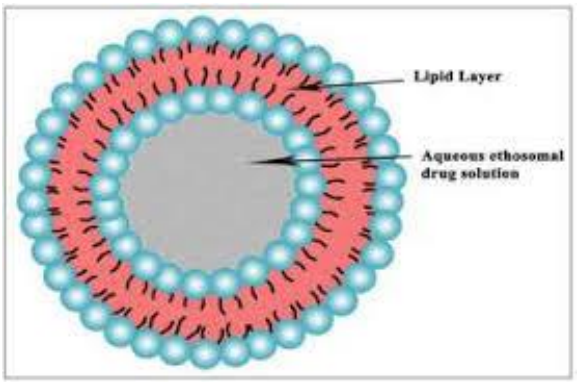

Figure 2. Structure of ethosome

Table 3. Examples of ethosomal herbal formulations

Biological source	Category	Active ingredient	Biological activity	Application
Glycyrrhiza glabra	Triterpenoid saponins category	Ammonium glycyrrhizinate	Treatment of dermatitis, eczema and psoriasis.	Improved anti-inflammatory activity and sustained release action
Curcuma longa	Resins	Curcumin	Anti inflammatory	Improved bioavailability
Cannabis sativa	Renin	Tetrahydro cannabi-diol (THC)	Treatment of rheumatoid arthritis	Improved patience compliance and skin penetration
Sophoraalo pecuroides	Quinazoline alkaloid	Matrine, oxymatrine, sophoridine,	Anti cancer	Increased permeability
Tripterygium wilfordii	Diterpine oxide	Triptolide	Anti inflammatory Anti tumor	Increased percutaneous permeability

Table 4. Examples of herbal Phytosome formulations.

Biological source	Active ingredients	Chemical classification	Biological activity	Application
Thea sinensis	Epigallocatechin-3-gallate, epigallocatechin, Epicatechin-3- gallate,	Polyphenols, Flavon-3-ol	Anti- oxidant and protective anti cancer	Increase in bioavailability
Curcuma longa	Curcumin, demethoxy curcumin and bisdemethoxy curcumin	Polyphenols	Anti oxidant and inflammatory	Improved bioavailability
Silybium marianum	Silibyn	Flavonoid	Hepato protective and anti oxidant	Increase in absorption
Vitis vinifera	Catechin, epicatechin	Proanthocyandins	Anti oxidant and anti cancer	Increase in anti oxidant property
Ginko biloba	Ginko flavones glucoside, ginkgolides, ginkgoic acids	Terpenoids	In cerebral insufficiency	Improve bioavailability
Panax ginseng	Ginseng	Saponins glycosides	Immune modulator	Inhibit lipid per oxidation

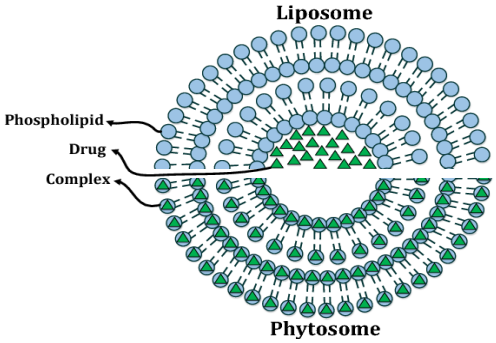

Figure 3 Difference between the structure of liposome and phytosome

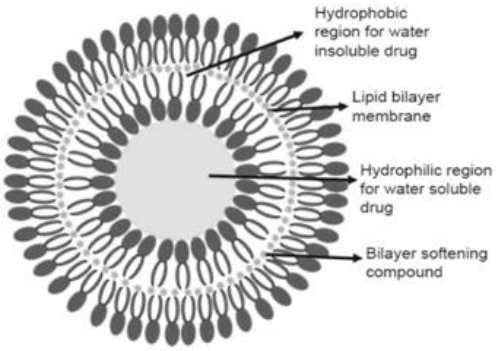

Figure 4. Structure of Transferosomes

Table 5.Examples of herbal transferosomes

Formulation	Active ingredients	Biological activity	Route of administration	Application
Capsaicin transferosomes	Capsaicin	Analgesic	Topical	Increase skin penetration.
Vincristine transferosomes	Vincristine	Anti cancer	in vitro	Increase entrapment efficiency and skin penetration.
Colchicine transferosomes	Colchicine	Anti gout	In vitro	Increase skin penetration.

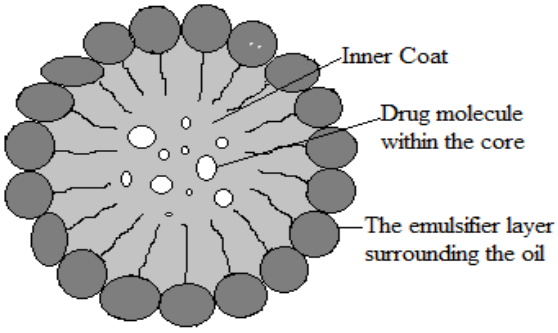

Figure 5. Structure of nanoemulsion

Table 6. Examples of emulsion herbal formulations

Formulation	Active ingredient	Method of preparation	Route of administration	Biological activity	Application
Silybin nano emulsions	Silybin	Emulsification method	Intramuscular	Hepatoprotective	Sustained release formulation.
Quercetin micro emulsion	Quercetin	High speed homogenization method	Topical	Anti oxidant	Enhance penetration into stratum corneum and epidermis.
Berberine nanoemulsions	Berberine	Drawing ternary phase diagram	Oral	Anti cancer	Improve residence time and absorption
Triptolide micro emulsion	Triptolide	High speed homogenization method	Topical	Anti inflammatory	Enhances the penetration of drugs

Table 7 Herbal solid-lipid nanoparticle formulations

Bioactive compound	Pharmacological action	Application
Curcumin	Anti-tumor, anti oxidant and anti inflammatory	Increase in stability
Curcuminoids	Anti malarial activity	Increase in activity

Table 8. Microsphere herbal formulations

Formulation	Active ingredient	Size in µm	Route of administration	Biological activity	Application
Quercetin microspheres	Quercetin	6	in vitro	Anti cancer	Significant decreases dose size.
Cynaras colymus microspheres	Cynaras colymus extract	6-7	Oral	Nutritional supplement	Continuous release of neutraceuticals.
CPT loaded microspheres	Camptothecin	10	Intra peritoneal and intravenously	Anti cancer	Prolonged release of camptothecin.
Zedoary oil microspheres	Zedoary oil	100-600	Oral	Hepato protective	Sustained release and higher bioavailability.
Rutin- alginate-chitosan microspheres	Rutin	165.0-195.0	in vitro	Cardio vascular diseases	Targeting into cardio vascular

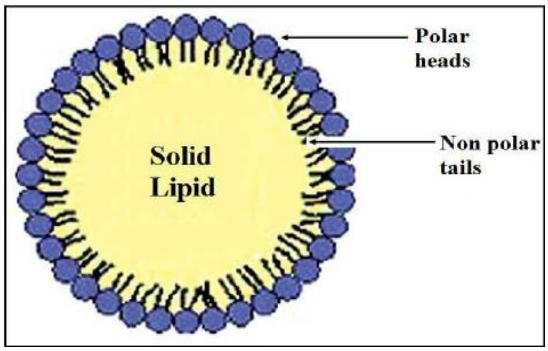

Figure 6. Structure of solid-lipid nanoparticles

SOLID-LIPID NANOPARTICLES

Nanoparticles are nanosized structures composed of synthetic or semi-synthetic polymers. Nowadays, nanoparticles of herbal medicines have engrossed much attention. Nanoparticles are colloidal systems with particles varying in size from 10 nm to 1000 nm. It is an effective system as the formulation is encapsulated in it easily and can easily reach the target site. 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. It is a colloidal carrier used especially for the delivery of lipophilic compounds. The structure of solid-lipid nanoparticle is shown in the Figure 6.

MICROSPHERES

Microspheres are discrete spherical particles ranging in average particle size from 1 to 50 µ [9]. Microencapsulation is a useful method which extends the duration of drug effect significantly and improves patient compliance. In some cases can even provide organ-targeted release. Micro particulate drug delivery systems are studied and taken on as a reliable one to rescue the drug to the target site with specificity, to assert the desired concentration at the situation of interest without untoward effects. Immune microsphere possesses the immune competence as a result of the antibody and antigen was coated or adsorbed on the polymer microspheres. Various herbal microsphere formulations are listed in Table 8.

FUTURE ASPECTS OF HERBAL DRUGS

Recently, herbal drugs have been getting more attention among scientists for the development of formulations, either classical or novel dosage forms. Public demand has also grown for evidence on the safety, efficacy and quality of herbal products and TM/CAM practices. 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. Fortunately, quite extensive phytochemical and pharmacological researches on medicinal plants and herbal medicines are already in place throughout the world and efforts are being made to isolate and identify their active chemical constituents and to substantiate the claims of their efficacy and safety. Scientific evidence from randomized clinical trials is also quite strong for use of many herbal medicines. The combination of drug delivery technology and herbal medicines provides a safe and effective therapy for human beings.

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. Poor solubility in water and bioavailability has limited the therapeutic efficacy of naturally available potential natural plant products. Research at great extent is going on in the area of development of novel drug delivery and targeting system for herbal drugs. The novel herbal drug delivery system will not only increase the market of herbal drugs but will also play a major role in providing better and effective therapy to humans.

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REFERENCES

1. Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010 ;81(7):680-9.
2. Solecki RS. Shanidar IV, a Neanderthal flower burial in northern Iraq. Sci. 1975;190(4217):880-1.
3. El-Samaligy MS, Afifi NN, Mahmoud EA. Evaluation of hybrid liposomes-encapsulated silymarin regarding physical stability and in vivo performance. International journal of pharmaceutics. 2006;319(1-2):121-9.
4. Ajazuddin, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. Elsevier B.V.; 2010; 81(7):680–9.

5. Yan-yu X, Yun-Mei S, Zhi-Peng C, I-Neng P. Preparation of silymarinproliposome: A new way to increase oral bioavailability of silymarin in beagle dogs. Int J Pharm 2006;319:162-8
6. Yanyu X, Yunmei S, Zhipeng C, Quineng P. The Preparation of Silybin-Phospholipid Complex and the Study on Its Pharmacokinetics in Rats. Int J Pharm. 2006; 307:77-82.
7. Cevc G, Blume G. New, highly efficient formulation of Diclofenac for the topical, transdermal administration in ultra-deformable drug carriers. TransferosomesBiochemBiophysActa. 2001; 1514:191–205.
8. Singh HP, Utreja P, TiwaryAK, Jain S. AAPS J 2009; 2:54–64.
9. 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.