

Herbal Drug Delivery System: A Modern Era Prospective

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ABSTRACT

Plant based medicines are used from ancient time for treatment of diseases. In some cases desirable effect are not achieved because the biological action of herbal medicine is due to phytoconstituents which can vary batch to batch. The amount of phytoconstituent in a plant can vary according to age of plant, time of collection, environmental condition etc. To overcome this problem standardized medicinal plants, plant extracts and isolated constituents can be used. But in case of most of herbal medicine stability as well as absorption is the limiting factor. Novel drug delivery system (NDDS) play very important role to overcome above mentioned issues. Moreover the patient compliance also increases.

Key Words: Herbal drug delivery, NDDS, Novel drug delivery system, Advance drug delivery system.

INTRODUCTION

From the history of civilization herbal medicines were used to cure human ailments in every possible condition. In modern era we have the option to use them over the synthetic molecules because herbal drugs have lesser side effects^{1, 2}. From the literature it is very clear that herbal drugs show their pharmacological action either due to specific constituent or due to blend of constituents. But the amount of constituents varies batch to batch due to ecological factors, time of collection of plant. Pharmacological effect of the drug can be obtained only when its concentration ranges within the therapeutic range. Any fluctuations above or below the therapeutic concentration lead to either toxic effects or no response. So the titration of dose as well as the determination of dose is necessary. To overcome such cases and to enhance the efficacy of the herbal drug Novel Drug Delivery System (NDDS) play important role, which is a unique blend of various branches of science such as polymer technology, pharmaceuticals, immunology, molecular biology, etc³. The Professionals of the field to understand the problems associated with the use of herbal products (such as, Poor stability in gastric environment, high extent of first pass metabolism, etc.) which creates a hindrance in their frequent usage over synthetic molecules by the use of nano technology, where vesicular systems helps in targeted delivery of the desired constituents⁴. Rate and extent are the two most important parameters among the drug delivery plus if they are supplemented with oriented drug delivery, the efficacy of the therapy increased a lot. Among various potentials of herbal NDDS the noteworthy are:

a) They can enhance the solubility of the constituents.

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- b) They can minimize the associated toxic effects.
 c) Improvement in pharmacological actions.
 d) Because of lipoidal content the tissue macrophage uptake of the constituents can also be enhanced.

Table 1 Herbal Formulations Based On Liposomal Drug Delivery System

Sr. no.	Plant / Constituents	Biological activity	Application of Liposomal technology	Reference
1	Ampelopsin	Anti cancer	Improved therapeutic outcomes	6
2	<i>Atractylodes macrocephala</i>	Digestive disorders and anti cancer	Enhancement of solubility and bioavailability	7
3	Capsaicin	Analgesic	Prolong action, permeation enhancement	8
4	Curcumin	Anti cancer	Long systemic residence time and high entrapment efficiency	9
5	Garlicin	Lungs	Enhanced therapeutic outcomes	10
6	Magnolol	Vascular smooth muscle proliferation inhibition	Efficacy enhancement	11
7	<i>Myrtus communis</i>	Anti microbial and anti oxidant	Activity enhancement	12
8	Nux vomica	Anti neoplastic, anti inflammatory and analgesic	Improved stability	13
9	<i>Origanum dictamnus</i>	Digestive disorders	Efficacy enhancement	14
10	Paclitaxel	Anti cancer	Sensitivity towards pH and improved entrapment efficiency	15
11	Puerarin	Anti oxidant and anti hypercholesterolemic	Enhanced efficacy	16
12	Quercetin	Anti congestion and anti anxiety	Improved efficacy, improved bioavailability and side effect reduction	17
13	Quercetin and Rutin	Hemoglobin	Hemoglobin binding enhancement	18
14	<i>Tripterygium wilfordii</i>	Anti cancer	Improved stability	19
15	Usnic acid	Anti mycobacterial	Prolong action and solubility enhancement	20
16	Wogonin	Anti cancer	Prolong duration of action	21

Table 2 Herbal Formulations Based on Nanoparticle Drug Delivery System

Sr no	Plant/ Constituents	Biological activity	Application of Nanoparticulate technology	Reference
1	Artemisinin	Anti cancer	Bioavailability enhancement and sustained drug delivery	23
2	Berberine	Anti cancer	Inhibition of <i>Helicobacter pylori</i> growth	24
3	Breviscapin	Cerebrovascular and cardiovascular	Prolong half life	25
4	Camptothecin	Anti cancer	Prolong circulation and high density around tumor containing area	26
5	<i>Cuscuta chinensis</i>	Anti oxidant and liver protective	Solubility enhancement	27
6	<i>Ginkgo biloba</i>	Brain activator	Metabolism and cerebral blood flow improvement	28
7	Ginseng	Anti oxidant	Improved Stability and pharmacological response	29
8	Glycyrrhizic acid	Anti hypertensive and anti inflammatory	Bioavailability enhancement	30
9	Hypocrellins	Anti viral	Improved efficacy, hydrophilicity and stability	31
10	Paclitaxel	Anti cancer	Sustained action and minimization of side effects	32
11	Paclitaxel and doxorubicin	Anti cancer	Lesser chances of resistance development	33
12	Quercetin	Anti oxidant	Improved therapeutic outcome and release enhancement	34
13	<i>Radix Salvia Miltiorrhiza</i>	Anti anginal	Bioavailability enhancement	35
14	Silibinin	Hepatoprotective	Improved entrapment and stability	36
15	Silybinin	Hepatotoxicity treatment	Enhanced circulation	37
16	Tetrandrine	Lungs	Sustained release of drug	38
17	Naringenin	Hepatoprotective	Solubility enhancement and improved release of drug	39

18	Zedoary turmeric oil	Liver protective, Anti oxidant and anti neoplastic	Improved stability and improved loading of drug	39
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- e) Sustained, controlled and targeted effect can also be achieved.
- f) Environmental degradation Prevention. It may be inside the body or outside; related physical and chemical degradations can be prevented⁵.

Note worthy systems are liposomes, phytosomes, transferosomes, ethosomes, nanoparticles (nanocapsules, nanospheres and solid lipid nanoparticles), microspheres, transdermal patches, implants and emulsions. The present review deals with the role of NDDS with special reference to herbal drugs/ phytomedicines.

LIPOSOMES

Liposomes are spherical, colloidal bilayered vesicular systems made up of biodegradable material i.e. Phospholipids. Phospholipids are the main structural units of these vesicles. They are an amphipathic molecules having bipolarity in their structure. Due to this, upon hydration with aqueous media they adopt a characteristic spherical shape and construct an aqueous core with in them. The polar head of phospholipid orient itself towards the aqueous media while the hydrophobic tails constitutes the inner region of the membrane. From here we can see that there is both hydrophilic region as well as hydrophobic region within the liposomal vesicle. This property made them a versatile carrier system as they can entrap both hydrophilic as well as hydrophobic drug with in it. Lipophilic drug occupies the lipoidal domain with in the bilayered membrane while hydrophilic drug occupy the aqueous domain i.e. aqueous core. Average size of liposome varies from 0.05 μ -5.0 μ . Among various advantages associated with liposomes the noteworthy are:

- Solubility enhancement
- Enhancement of bioavailability
- Programmed targeting
- Prolongation of duration of action
- As they are lipoidal in constitution they enhance the tissue macrophagial uptake of the entrapped constituents.
- Stability associated problems can also be solved
- Absorption and disposition of the constituents can also be tailored⁶.

Enormous research has been done in this field (Table 1) and still their marvelous applications inspire researchers to ripe more benefits from this drug delivery system.

NANOPARTICLES

They are the nanosized particulates (10 nm -1000nm) which can be nanospheres, nano capsules or Solid Lipid Nanoparticles (SLNs). Nanospheres are matrix based systems in which the drug uniformly dispersed in the carrier matrix. The matrix can be either synthetic or natural. Among synthetic generally biodegradable polymers are used which are Generally Regarded as Safe (GRAS) by FDA for human consumption. The examples include polylactic acid, poly- α - cyanoacrylate alkyl esters, polyvinyl alcohols, glycolic acid polymers, etc.

Among natural polymers that are use as matrix in nano particulates, there are two important categories: (a)

Table 3 Herbal Formulations Based on Phytosomal Drug Delivery Systems

Sr. no.	Plant/ Constituent	Biological activity	Application of Phytosomal Technology	Reference
1	Curcumin	Anti cancer and Anti oxidant	Improved anti oxidant activity and bioavailability	42
2	Embelin	Anti fertility and anti Bacterial	Solubility enhancement	43
3	Epigallocatechins	Anti cancer and anti oxidant	Absorption enhancement	44
4	<i>Ginkgo biloba</i>	Anti asthmatic, anti diabetic and cardio protective	Improved efficacy	45
5	Ginsenosides	Immuno modulator and neutraceutical	Absorption enhancement	46
6	Hawthorn	Cardio protective and anti hypertensive	Improved efficacy and absorption	46
7	Marsupium	Anti viral	Bioavailability enhancement	47
8	Naringenin	Anti cancer and anti inflammatory	Prolong action and enhanced bioavailability	48
9	Oxymatrine	Anti viral	Bioavailability enhancement	49
10	Procyanidins	Cardio protective Anti oxidant	Increased total radical trapping antioxidant parameter (TRAP)	46

Polysaccharides (chitosan, cellulose and its derivatives, dextran, alginate, etc.) and (b) Proteins (gelatin, albumin and several types of proteins from vegetative origin)

In case of nano spheres the drug release is controlled by two parameters namely, dissolution and diffusion. There release can show a burst release mechanism as well as surface erosion mechanism. Nano capsules contrary to nano spheres are reservoir type system in which the drug core is surrounded by a polymeric membrane. While SLNs are specifically designed to give programmed delivery of lipoidal drugs with in the body. Various methods are there for their preparation like solvent diffusion methods, warm micro emulsion formation method, sonication method, etc. Associated research in this field related to the herbal drugs is listed in (Table 2). Various advantages of nanoparticles include:

- a) Enhanced shelf life of product
- b) Possibility of tailoring surface characteristics
- c) Enhancement of solubility
- d) Minimization of adverse reaction associated with dose
- e) Targeting to specific locus in the body
- f) Hydrophilic as well as lipophilic both type of drugs can be incorporated²².

PHYTOSOMES

Table 4 Herbal Formulations Based on Microsphere Drug Delivery Systems

Sr. no.	Plant/ Constituent	Biological activity	Application of Microsphere Technology	Reference
1	Camptothecin	Anti cancer	Dose reduction	54
2	Ginsenosides	Anti cancer	Solubility and stability improvement	55
3	<i>Piper sarmentosum</i>	Anti diabetic	Easy for industrial scale up	55
4	Quercetin	Anti inflammatory and anti oxidant	Permeation enhanced	56
5	Rutin	Anti oxidant	Specific delivery to heart and brain vascular systems	57
6	Silymarin	Treatment of Liver diseases	Sustained release of medicament Improved patient compliance	58

Table 5 Herbal Formulations Based on Emulsion Systems

Sr. no.	Plant/ Constituents	Biological activity	Application of Emulsion Technology	Reference
1	<i>Azadirachta indica</i>	Acaricidal, anti bacterial And anti fungal	Reduction in associated adverse reactions	62
2	Berberine	Anti cancer	More residence time in the body	62
3	Curcumin	Anti cancer	Improved absorption	63
4	Docetaxel	Anti cancer	More residence time in the body	64
5	Matrine	Anti inflammatory and anti bacterial	Sustained release of medicament	65
6	Quercetin	Anti oxidant	Permeability enhancement	66
7	Rhubarb	Luxative and cathartic	Therapy improvement	66
8	Zedoary turmeric oil	Liver protective, anti cancer and anti Bacterial	Dispersibility, stability and bioavailability enhancement	67

They are bilayered system designed for the delivery of those drugs from which proper therapeutic outcomes can not be leached because of either of their high molecular weight or of their polar nature (e.g. flavonoids).

Phytosomes helps in overcoming these limitations in drug delivery so as to enhance the bioavailability of such chemical entity. They involve binding of drug molecules to phospholipids (phosphatidyl choline) in a stoichiometric ratio (1:1 or 1:2) so as form lipid complexes⁴⁰. As they involve the bond formation they are more stable with respect to liposomes where there is only an entrapment of these constituents in the aqueous domain. They can entrap higher amount of drug, can over can the stability related issues, and enhances the cutaneous absorption. Use of phospholipids made them well suitable for use as phospholipids have natural origin. Like

Table 6 Herbal Formulations Based on Transferosomal Drug Delivery Systems

Sr. no	Plant/ Constituent	Biological activity	Application of Transferosomal Technology	Reference
1	Colchicine	Anti gout	Reduction in associated GIT side effects	69
2	Curcumin	Anti cancer and anti oxidant	Permeation enhancement	70

liposome generated both lipophilic as well as hydrophilic domains because of which they can entrap lipophilic as well as hydrophilic drugs⁴¹. Work have been done on various herbal drug for making their phytosomes to make the therapy more effective (Table 3) such as, oxymatrin, silybin, embelin, etc.

MICROSPHERES

They are spherical matrix based systems varying 1 μ - 300 μ in size, in which drug is uniformly dispersed in polymeric matrix. Various techniques that can be adopted in the synthesis of microspheres are single emulsion technique, double emulsion technique, Polymerization techniques (normal as well as interfacial), spray drying and spray congealing, phase separation coacervation method and solvent extraction technique^{50,51}. First ordered release kinetics is generally followed in such systems where the release rate limiting steps are diffusion and dissolution⁵². Firstly the outer dissolution media will diffuse the matrix make the entrapped drug to solublise in it and than the drug is released from the system this is one type of mechanism in other type the system constituting polymer show surface erosion behavior where the surface erode layer by layer and the release of drug occurs^{50,53}. There main factors are there which influence the released amount as well as its rate. They are:

- Size- Smaller the size more will be the surface area, lesser will be the path length to diffuse or lesser layers required to erode for drug release.
- Type of matrix – It depends on way in which matrix show its release
- Polymer concentration- It is inversely proportional to the amount of drug released.

Microspheres have various advantages which make them a suitable carrier for drug delivery. Noteworthy among them are:

- Their ingestability and injectability
- Ability to give sustain release profile
- Specificity towards a particular locus with in the body (immuno microspheres)^{50,52,53}

All these things ultimately lead to minimization of side effects and improving the efficacy of the therapy. Zedoary turmeric oil, rutin, camptothecin, etc. are some examples of drugs give by microsphere drug delivery (Table 4).

EMULSION BASED SYSTEMS

Emulsion is a biphasic dispersion system in which both the dispersed phase and the dispersion medium are liquid the globules are stabilized in the dispersion media with the aid to surfactants which act on the interface between two phases and there by minimizing the interfacial energy so as to stabilize the system and to prevent

Table 7 Herbal Formulations Based On Ethosomal Drug Delivery Systems

Sr. no.	Plant/ Constituent	Biological activity	Application of Transfersomal Technology	Reference
1	Matrine	Anti inflammatory, anti cancer, anti rheumatism and anti bacterial	Permeation enhancement and improved efficacy	72
2	<i>Sophora alopencerides</i>	Anti cancer, Anti endotoxic	Permeation enhancement	73
3	Triptolide	Anti inflammatory	Bioavailability enhancement	74

coalescence^{59,60}. Surfactants can be cationic, anionic and non ionic. Only those surfactants are used in the preparation of consumable emulsions which are regarded as safe by FDA. Based on globule size emulsion system is further classified into 4 categories namely ordinary emulsion, micro emulsion, nano emulsion and sub micro emulsion (lipid Emulsion)^{60,61}. Globule size order is ordinary (0.1 μ -100 μ) > sub micron (100 nm- 600nm) > micro (10nm- 100 nm)⁶⁰. Emulsion based systems have various advantages which made them a suitable carrier system for herbal drug delivery (Table 5) ranging from specific locus targeting to sustained release, enhanced macrophagial uptake to minimization of stability issues, increased permeability of herbal constituents etc.

TRANSFEROSOMES AND ETHOSOMES

Transfersomes and Ethosomes are phospholipid vesicles intended to administer the drug via transdermal route. Both have a common rationale of enhancing the penetration through stratum corneum barrier but the mode of action is different⁷⁰. Transfersomes do so by utilizing the hydration and osmotic pressure of the skin while in case ethosomes they have high content of ethanol (20- 45%). Ethanol being a chemical permeation enhancer disrupts the membrane barrier and there by enhance the solubility. Moreover, it makes the vesicle flexible without altering the stability component associated. Transfersomes are used to deliver the herbal constituents in the upper layers of skin while for deeper layer and systemic delivery ethosomes are the better alternative. Usually they are give in the form of cream or gel, being non invasive they have better patient compliance^{68, 71}. There are enormous examples where efficacy of herbal constituent mediated treatment is increased by adopting these delivery systems (Table 6 and 7). E.g. colchicine, curcumin, matrine, triptolide, etc.

OTHER NOVEL DRUG DELIVERY SYSTEMS

They include transdermal drug delivery with the aid of patches, implant based drug delivery and micro pellets. Reports show that they can also be a good means of drug delivery of herbal constituents to improve the efficacy of the therapy. Transdermal drug delivery system is a non invasive means of drug delivery which can be of either monolithic type or reservoir type. They are supposed to release drug at a predetermined rate over the site of application. Among their advantages note worthy are their ability to control the release, possibility of withdrawal of therapy if required, ease of use and ability to prolong the duration of action⁷⁵. They can even incorporate the vesicular system with in them. For example, delivery of a synergistic combination of boswellic

acid (*Boswellia serrata*) and curcumin (*Curcuma longa*) has been prepared and evaluated and these systems were found to enhance their anti-inflammatory effects⁷⁶. Implants are biodegradable units meant to be placed

Table 8 Herbal Formulations Based on Micropellatization Drug Delivery Systems

Sr. no.	Plant/ Constituents	Biological Activity	Application of Micropellatization Technology	Reference
1	Andrographolides	Rheumatoid arthritis treatment	Improved stability in GIT and reduction in GIT irritation	78
2	Curcumin	Anti inflammatory	Sustained Release and targeting to specific locus	79

under the skin layers with the aid of micro surgery, where they are supposed to give the sustained action. For example, implant of Danshen (*Radix Sliciae Miltiorrhizae*) by utilizing gelatin and chitosan as a matrix polymers. Micro pellets are another type of matrix system having a size range of 1 μ -1000 μ . They can reduce the repeated dosage administration, orient the delivery to specific site, can overcome the problem of delivery of two incompatible materials simultaneously and can also be exploited for the purpose of taste masking⁷⁷. Herbal micropellatization technologies are listed in (Table 8).

MARKETED HERBAL NOVEL DRUG DELIVERY FORMULATIONS

Two companies dominate the market for these systems viz. Cosmotech and Indena. For herbal drug delivery Cosmotech launches Herbasec[®] technology in marketed which are actually liposomal preparations of various herbal constituents like extracts of White tea, Green tea, white hibiscus, Gurana and Aloe vera. These extracts are used in cosmetics because of their anti oxidant effects for prevention of aging. Indena patented the technology of phytosomes[®] and launches many products in market under this having diverse therapeutic benefits. Indena commercializes the plant constituents/ extracts of liquorice (18 β -glycyrrhetic acid), *Ammi visnaga* (visnadin), *Centella asiatica* (triterpenes), *Ginkgo biloba* (ginkgoflavonglucosides, ginkgolides, bilobalide), Hawthorn flower (vitexin-2''-O-rhamnoside), milk thistle (silymarin and Silybin), horse chestnut (escin β -sitosterol), *Terminalia sericea* (sericoside), *Panax ginseng* (ginsenosides), grape seed (polyphenols), Green tea (polyphenols), etc^{80,81}.

FUTURE ASPECTS

Many other novel drug delivery systems can be utilized to enhance the efficacy of herbal medicines⁸⁰. Sublingual dissolving tablets can be used for the administration of phytoconstituents for quick onset of action, since sublingual mucosa is rich in blood supply, drug directly bypass the first past metabolism which is the main problem associated with the herbal drugs. Mucoadhesive drug delivery system can also be utilized to enhance the efficacy of the therapy, reason is that whether the drug delivery is in the form of unit dosage form or multiparticulate system it makes the dosage form to locate itself around the absorption window of the drug molecule which may lead to the enhancement of bioavailability⁸². Floating drug delivery yet another approach which can be used in the case of the drugs having absorption in the upper GI tract. Its utilization is limited since most of the herbal drugs are unstable at gastric pH^{57,81}. Niosomes can also be used to deliver the herbal drugs⁸².

They are cheaper than liposomes, due to the use of non ionic surfactants the associated toxicity of the carrier system is less with respect to ionic surfactants. They don't have issues related to oxidation, etc. as associated with liposomes because liposome contains lipids which contain double bounds in their structure. They are prone to free radical chain mediated oxidation reactions. Above mentioned examples are the few among various other types of NDDS which are still pending to be utilized for the delivery of herbal molecules. Targeting is another domain can be utilized to increase the therapeutic efficacy of the delivery system⁸³.

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