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NOVEL DRUG DELIVERY SYSTEM FOR HERBAL FORMULATION IN CANCER TREATMENT

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ABSTRACT

Plant products have been used since in ancient times for various purposes. Nowadays, plants are being used as natural remedies for the treatment of various health concerns like allergies, wounds, burns, gastrointestinal disorders and even for cancer- (which proves food is medicine). Herbal drugs are good to use but difficult to process, identify, extract and deliver, thereby it needs modifications in order to overcome these problems, leading to the development of Novel Drug Delivery System (NDDS). NDDS is also beneficial in comparison to conventional methods for cancer treatment. It has modified the herbal drugs to increase their therapeutic value, reduce toxicity, achieve sustained and controlled release, improve solubility, bioavailability and increase patient compliance. NDDS includes various novel carriers like liposomes, phytosomes, microspheres, microemulsions, transferosomes, ethosomes and solid-lipid nanoparticles. The purpose of this review is to outline several NDDS for delivery of herbal drugs for cancer treatment.

KEYWORDS: Liposomes, phytosomes, microspheres, microemulsions, transferosomes, ethosomes and solid-lipid nanoparticles.

1. INTRODUCTION

Herbal medicines have been widely used around the world since ancient times. The use of ‘herbs’ in the treatment of various diseases with fewer side effects has significantly increased.[1] Phytoconstituents are the plant constituents used in herbal medicines which are responsible for the biological action. Since the biological activity of the plant varies from batch to batch and thus, desirable effects are not achieved. Phytoconstituents are also required

for standardization of herbal molecules. It depends on the age of the plant, time of collection, environmental condition, etc.[2] Various classes of phytoconstituents are alkaloids, flavonoids, tannins, essential oils, etc. These phytoconstituents are water-soluble but are big molecules and hence not able to cross the lipid membrane and thus they show poor absorption. Limitations of using natural products as medicines are stability, absorption and therapeutic effects which can be overcome by Novel Drug Delivery Systems which includes technologies, formulations and approaches to deliver a drug as needed to safely achieve the desirable effects.[3] Nanomedicine involves utilization of Nanotechnology for the human health welfare.

Nanotechnology is science, engineering, and technology conducted at the nano-scale (1-100 nm). Researchers are developing drug carrier of the size of molecule that can deliver drug specifically to the diseased cells in the body. Conventional drugs suffer some adverse effect due to its non-specificity of drug action and improper or ineffective dosage formulations. We can design drugs with greater efficacy and cell specificity to minimize adverse effects by using nanotechnology. Nanoparticles are one of the significant Novel drug delivery systems. The effective delivery of herbal medicines can be achieved by novel formulation of nanoparticles such as liposomes, solid-lipid nanoparticles, microemulsions, ethosomes and polymeric nanoparticles with herbal molecules for better therapeutic effect, selectivity, effectiveness, the bioavailability of drug at target site which thereby reduces the dosing frequency and thus the healthcare cost. A liposome is a small vesicular drug delivery system which can carry both hydrophilic and lipophilic drugs. It is non-toxic, biodegradable and biocompatible vesicle. Liposomes are made up of polar lipids.[4] Phytosomes are little cell-like structure and are an advanced form of the herbal formulation, phytosomes are prepared by the patented process by forming a complex of active herbal formulations and lipid, preferably phosphatidylcholine resulting in better absorption of the drug.[5] Other novel drug delivery system like transferosomes, ethosomes, solid-lipid nanoparticles, microspheres enhance the bioavailability, solubility, biocompatibility of the herbal formulations with many other advantages. For better utilization of all above-stated benefits, we need an ideal nanoparticulate system which has better availability in blood and is small enough to reach the target cells.[6,7]

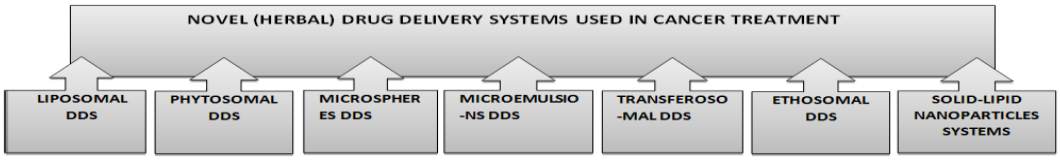
1.1 Types of nanoparticles used for drug delivery in cancer treatment

- Carbon magnetic nanoparticles

- Dendrimers
- Ceramic nanoparticles
- Chitosan nanoparticle
- Liposomes
- Low-density lipoprotein
- Nano- emulsion
- Micelles
- Nano spheres
- Nano vesicles
- Nano liposphere

2. Types of herbal nanoparticles used in cancer treatment

- Liposomal Drug Delivery Systems
- Phytosomal Drug Delivery Systems
- Microspheres Drug Delivery Systems
- Microemulsions systems
- Tranfersomal Drug Delivery Systems
- Ethosomal Drug Delivery Systems
- Solid-Lipid Nanoparticles systems



2.1 LIPOSOMAL DRUG DELIVERY SYSTEMS

Liposomes are ideal drug delivery system because its morphological structure resembles with cell membrane structure. Liposomes are spherical vesicles made up of phospholipid bilayer used as colloidal vesicular drug delivery systems.[8] Phospholipid molecules are amphipathic in nature having a hydrophilic head and hydrophobic tail, which in contact with water forms a spherical vesicle with head aligned towards the aqueous region and tails entrapped in membrane, forming an aqueous core (aqueous domain) which can accommodate hydrophilic drugs and lipoidal domain entrapped in bilayer-membrane which accommodates hydrophobic drugs i.e. it can carry both hydrophilic and hydrophobic drugs.[9] The average size of liposome ranges from 0.05 to 5.00 micrometer.[10]

Liposomes can act as potential drug delivery system for cancer treatment due to its ability to reduce the side effects caused by non-selective nature of cancer treatment methods by increasing specificity for cancer cells. It has an ability to promote passive targeting of cancer cells. Tumour-specific cells have increased permeability and retention effect due to which larger molecules can enter inside it, this nature of cancer cells allows liposomes loaded with anticancer drugs to enter inside the cancer cells, but same are restricted by endothelial walls to enter in healthy cells. As a result of this, the drug-loaded liposomes are targeted to tumor cells only not to the healthy cells, this property is called passive targeting.[11]

Advantages of liposomes include,

- Enhanced Solubility
- Non-toxicity
- Enhanced Biodegradability
- Sustained delivery
- Enhanced Stability
- Enhanced Bioavailability
- Highly biocompatible

Table-1: Herbal formulations based on liposomal drug delivery systems.

Ser No	Plant/constit-uent used	Derived from plant	Biological activity	Application of technology	Ref
1	Ampelopsin	Ampelopsis species japonica, megalophylla and grossedentata	Anticancer	Improved therapeutic outcomes	[12]
2	Root of *Atractylodes macrocephaa*	*Atractylodes macrocephala* (sunflower family)	Digestive disorders and Anticancer	Enhancement of solubility and bioavailability	[13]
3	Curcumin	Turmeric(*Curcuma longa)*	Anticancer	Long systemic residence time and high entrapment efficiency	[14]
4	Nux Vomica	Strychnos nux-vomica	Anti-neoplastic, anti-inflammatory, and analgesic	Improved stability	[15]
5	Paclitaxel	Derived from the bark of the Pacific yew tree (Taxus brevifolia)	Anticancer	Sensitivity towards pH and improved entrapment efficiency	[16]
6	Triptolide (active compound)	*Skinned root of Tripterygium wilfordi*	Anticancer	Improved stability	[17]
7	Wogonin	*Scutellaria baicalensis Georgi*	Anticancer	Prolonged duration of action	[18]

2.2 PHYTOSOMAL DRUG DELIVERY SYSTEMS

Phytosomes are cell-like small structure and advanced form of herbal formulation. It is made up of bioactive phytoconstituents of herbal extract surrounded by the lipid bilayer, consisting of phosphotydicholine. Phytosomes show better stability profile because phosphatidylcholine molecules and phytoconstituents are chemically bonded. Bioactive phytoconstituents possesses broad therapeutic activities and includes flavonoids (major), glycosides, terpenoids etc.[19] Phosphotydylcholine has gastro-protective properties and hence plant extracts (drugs) are protected from destruction in GI tract, hence exhibit better pharmacokinetic and pharmacodynamic profile with improved bioavailability than conventional herbal_extract. It has both lipophilic and hydrophilic drug domains so it can carry both types of drugs. Flavonoids are major and important groups of phytochemical and these are also known as nature's biological response modifier because they show the anti-inflammatory, anti-allergic, antiviral and anti-cancer properties.[20]

Advantages of Phytosome include:

- High lipophilicity
- Enhanced bioavailability
- High stability

Table-2: Herbal formulations based on phytosomal drug delivery systems.

Ser no	Plant /constituent used	Derived from plant	Biological activity	Application of technology	Ref.
1.	Curcumin	Turmeric (*Curcuma longa*	Anticancer and Anti-oxidant	Improved antioxidant activity and bioavailability	[21]
2.	Epigallocatechin	Green tea	Anticancer and Anti-oxidant	Absorption enhancement	[22]
3.	Naringenin	Orange and grape juice	Anticancer and Anti-inflammatory	Prolong action and enhanced bioavailability	[23]
4.	Procyanidins	Grape seed	Anticancer and Anti-oxidant	Bioavailability enhancement	[24]

2.3 MICROEMULSIONS

Microemulsions are clear, thermodynamically stable, an isotropic mixture of oil and water, stabilized by surfactants and sub-surfactants. Small-scale emulsions, such as droplet-type dispersions, either oil in a water type (O/W) or water in oil type (W/O). Micro emulsion's size ranges from 5-100 nm. The aqueous phase contains salt and other ingredients and the oil

phase contains a mixture of hydrocarbons and olefins. O/W or O/W/O emulsion are made for oily or lipophilic drugs while W/O or W/O/W emulsion are prepared for water-soluble drugs.[25]

Advantages of micro-emulsion:

- Solubilisation capacity
- Sustained release of drugs
- High stability
- Simplicity of manufacture
- Bioavailability improvement

Table-3: Herbal formulations based on microemulsion drug delivery systems.

Ser no	Plant /constituent used	Derived from plant	Biological activity	Application of technology	Ref.
1	Curcumin	Turmeric (*Curcuma longa)*	Anti-tumour, anti-oxidant and antiplatelet aggregation	Enhance anti-inflammatory activity	[26,27]
2	Triptolide	Diterpenoid triepoxide obtained from Chinese medicine Tripterygium Wilfondil hook F	Used in the treatment of autoimmune disease especially leukemia and antineoplastic activity	Reduce the toxicity	[28]
3	Berberine	*Berberis vulgaris*	Anticancer	More residence time in the body	[29,30]
4	Docetaxel	European yew tree Taxus baccata	Anticancer	More residence time in body	[31,32]

2.4 MICROSPHERES

Microspheres are used as a vehicle for the controlled release drug delivery system. It is a matrix based drug encapsulating device in which drugs are uniformly dispersed in the polymer matrix and can encapsulate a variety of drugs.[33] It mainly consists of protein and polymer (Poly Lactic Acid (PLA), Polylactic-co-glycolic acid (PLGA), gelatine, albumin, polylactic etc. are some of the approved of polymers). Polymers may be natural or synthetic. The release of drug dispersed in polymer occur by first order process**.** Polymeric concentration is inversely proportional to the amount of drug release.[34] Size of microspheres ranges from 1µ to 300µ. They can be tailored for desired release profiles and used for site-specific delivery of drugs. Microspheres are ideal vehicles due to their high bioavailability, biocompatibility and sustained release characteristics.

Advantages of microspheres:

- Facilitate accurate delivery of small amount of potential drug
- Controlled release of drug
- Protect unstable drug
- Enhanced bioavailability

Table-4: Herbal formulations based on microsphere drug delivery systems.

Ser. No	Plant/constituent used	Derived from plant	Biological activity	Application of technology	Ref.
1.	Camptothecin	Bark and stem of *Camptotheca acuminata*	Anti-cancer	Dose reduction	[35]
2.	Quercetin	citrus fruits, apples, onions	Anti-cancer	Permeation enhanced	[36]
3.	Ginsenosides	genus *Panax* (ginseng)	Anti-cancer, antioxidative and anti-inflammatory	Solubility and stability improvement	[37]

2.5 TRANSFEROSOMES AND ETHOSOMES

Transfer some and ethosomes are novel and flexible vesicular drug delivery systems made up of phospholipid for transdermal delivery, by enhancing the skin permeation. Mode of action of both the phospholipid vesicles differs, tranferosomes use the hydration and osmotic properties of skin while ethosomes due to high ethanol content disrupt the membrane barrier and thus enhances the solubility and permeability.

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation while tranfersomes are used for delivering the drug in upper layers of skin. The size of Ethosomes vesicles can be modulated from tens of nanometers to microns.[38,39]

Advantages of transferosomes and ethosomes:

- Delivery of variety of drugs
- Permeation enhancement of skin
- Delivery of drugs in semisolid form

Table-5: Herbal formulations based on transferosomal drug delivery systems.

Ser. no	Plants used/ constituents	Derived from which plant	Biological activity	Application of Technology	Ref.
1.	Curcumin	Turmeric (*Curcuma Longa)*	Anti-cancer	Improved anti-oxidant activity and Bioavailability	[40]
2.	Colchicine	Genus *Colchicum*	Anti-cancer Anti-gout	Reduction in GIT side effects.	[41]
3.	Vincristine	*Catharanthus roseus*	Anti-cancer	Increase in permeability	[42]

Table-6: Herbal formulations based on ethosomal drug delivery systems.

Ser no	Plant used/ constituents	Derived from which plants	Biological activity	Application of technology	Ref
1.	Matrine	Sophora flavescens	Anti- inflammatory, anti-cancer, anti-rheumatism and anti-bacterial	Permeation enhancement and improved efficacy	[43]
2.	*Sophora alopencerides*	*Sophora alopencerides*	Anti-cancer, Anti endotoxic	Permeation enhancement	[44]
3.	Podophyllotoxin	Podophyllum hexandrum	Purgative, anti-rheumatic, antiviral and antitumor	Higher entrapment efficiency	[45]

2.6 SOLID-LIPID NANOPARTICLE

Solid-lipid nanoparticles are sub-micron colloidal system and its size ranges from 50-100 nm. It is prepared by dispersing the physiological solid lipids particles in nanometre range in water or in an aqueous surfactant solution. These are monolayer phospholipid carrier system having a solid hydrophobic core i.e. they have a tendency to carry lipophilic or hydrophilic drugs. SLNPs are biocompatible, non-toxic, biodegradable etc. SLNPs have long-term stability and better control over the release kinetics of encapsulated compound.[46]

Table-7: Herbal formulations based on solid-lipid nanoparticulate drug delivery systems.

Ser no	Plant used/ constituents	Derived from which plant	Biological activity	Application of technology	Ref.
1.	Triptoplide	extract of the Chinese herb *Tripterygium wilfordii* Hook F.	Used in the treatment of autoimmune disease especially leukemia and antineoplastic activity	Enhancement of bioavailability	[47,48]
2.	Curcuminoids	*Curcuma longa*	Antitumour, antioxidant Antiplatelet aggregation	Reduction of drug toxicity, enhancement of bioavailability	[49]
3.	Podophyllotoxin	Obtained from dried roots of *Podophyllum pellatum*	Antivirus and anticancer activity	Enhancement of bioavailability	[50]

3. FUTURE PROSPECTS

Nowadays, people are opting for herbal medicines for their better therapeutic values and lesser adverse effects, so there is a need to develop a novel drug delivery system and a targeting system for herbal drugs.[51] Novel drug delivery system, not only provides a safe and effective delivery, enabling people to regain faith over herbal drug delivery systems but also increases the market for herbal drugs. Several other novel drug delivery systems can be used for enhancing the efficacy of drugs.[52,53]

- Sublingual delivery of phytoconstituents, for rapid action of the drug as it bypasses the first pass metabolism which is the main problem of herbal drugs.
- Muco-adhesive Drug delivery can also be used for targeted delivery of drugs which increases the bioavailability of drug locally.
- Floating Drug delivery of drugs which are stable at gastric pH for their absorption in upper GI tract
- Niosomes can also be used in place of liposomes and are less toxic than liposomes since they have non–ionic carrier system. Unlike liposomes, they don't undergo any free radical oxidation.

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