Review Article

Novel Techniques in Herbal Drug Delivery Systems

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ABSTRACT

Phytomedicines are used worldwide by human being from ancient times. However these medicines suffer from certain limitation such as toxicity, stability issues, poor bioavailability and patient compliance. To minimize these problems various novel drug delivery systems (NDDS) such as phytosomes, ethosomes, transfersomes, herbal transdermal patches, nanoparticles and biphasic emulsions are used nowadays. With use of these advance techniques protection from toxicity, enhancement in stability, improved bioavailability of herbal formulations, protections from physical and chemical degradation can be achieved. These techniques provide improved patient compliance, sustained release and targeted action of plant actives and extracts. The present reviews gives information regarding various novel techniques used for improving safety and efficacy of phytomedicines, type of active ingredients, biological activity and application of novel formulation.

Keywords: Phytomedicines, Novel drug delivery systems (NDDS), Phytosomes.

INTRODUCTION

Herbal medicines are the oldest form of health care known to mankind.[1] World Health Organization (WHO) has defined herbal medicines as finished, labeled medicinal products that contain active ingredients, aerial or underground parts of the plant or other plant material or combinations.[2] WHO estimates that 80% of the world populations presently use herbal medicine for primary health care.[3]

Herbal preparation are obtained by subjecting whole plant, fragmented or cut plants, plant parts to treatment such as extraction, distillation, expression, fractionation, purification, concentration or fermentation.[4]

Herbal drugs have certain advantages over traditional medicines such as lower risk of side effects, widespread availability, low cost and efficacious for lifestyle diseases for prolonged period of time.[5] Also there is increasing evidence that many current drug therapies simply suppress symptoms and ignore the underlying disease processes. In contrast, many natural products appear to address the cause of many diseases and yield superior clinical results.[6]

But these herbal extracts/plant actives suffer from various limitations such as stability in highly acidic pH, liver metabolism etc. led to drug levels below therapeutic concentration in the blood resulting in less or no therapeutic effect.[7] Also most of the plant actives such as glycosides, tannins, flavonoids, etc. are polar in nature and poorly absorbed due to large molecular size limiting the absorption via passive diffusion, poor lipid solubility hence preventing their ability to cross the lipid-rich biological membranes. These limitations lead to reduced bioavailability and hence, low therapeutic index of plant actives.[8]

Hence considerable attention has been given to development of novel drug delivery system for herbal drugs. The novel carriers should ideally fulfill two requirements, 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.[9] Incorporating herbal drugs into novel drug delivery systems not only reduce the repeated administration to overcome non-compliance, but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability.[10] Novel drug delivery attempts to either sustain drug action at a predetermined rate or by maintaining a relatively constant effective drug level in the body with minimization of undesirable side effects. Various drug delivery technologies such as phytosomes, ethosomes, transfersomes, nanoparticle, herbal transdermal patches, micro and nanoemulsion have been developed for delivery of herbal actives/extracts which are gaining more attention for better therapeutic response.[11]

PHYTOSOMES

Phytosomes are lipid compatible molecular complex which are composed of "phyto" which means plant and "some" meaning cell-like.[12] Most of the bioactive constituents of phyto-medicines are water-soluble molecules such as phenolics, glycosides, and flavonoids. However, these are limited in their effectiveness because of poor absorption when taken orally or when applied topically as it cannot penetrate lipoidal membrane barrier.[13] Phytosome is a patented technology developed

by a leading manufacturer of drugs and nutraceuticals, it incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes improving their absorption and bioavailability.[14]

The Phytosomes process produces a little cell to protect the valuable components of the herbal extracts from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the hydrophobic environment of the cell membrane and from there into the cell finally reaching the blood. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions.[15]

ETHOSOMES

Transdermal administration of drugs is generally limited by the barrier function of the skin. Vesicular systems are one of the most controversial methods for transdermal delivery of active substances.[20]

Ethosomes are interesting and innovative vesicular systems that have appeared in the field of pharmaceutical technology and drug delivery in recent years. This carrier presents interesting features correlated with its ability to permeate intact through the human skin due to its high deformability. It has been shown that the physicochemical characteristics of ethosomes allow this vesicular carrier to transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposomes. Ethosomes entrap drug molecule with various physicochemical characteristics i.e. of hydrophilic, lipophilic, or amphiphilic.[21]

Ethosomes are soft, malleable non-invasive vesicles for enhanced delivery of active agents. It is of great importance for the design of phytomedicine to be applied topically both for topical and systemic drug administration. The size range of ethosomes may vary from tens of nanometers (nm) to microns (µ).[22]

Ethosomes are lipid based elastic vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. High concentration of ethanol enhances the topical drug delivery and prolongs the physical stability of ethosomes with respect to liposomes.[23]

Table 1: Herbal Phytosome Formulations.[16-19]

Biological Source	Category	Application	Use	Active ingredients
Silibium marianum	Flavonoids	Increase in absorption upto 4.6 folds	Hepatoprotective, Antioxidant.	Silybin
Vitis vinifera	Proanthocya-ndinis	Increase in antioxidant property	Antioxidant, Anticancer.	Catechin, epicatechin
Curcuma longa	Polyphenols	Increase in bioavailability	Antioxidant, Antiinflammatory, Anticancer	diferuloylmethane curcumin, demethoxycurcumin and bisdemethoxy-curcumin
Thea sinensis	Polyphenols, Flavon-3-ol	Increase in bioavailability of epigallocatechingallate	Anti-cancer, Antioxidant, Cardiovascular, neuroprotective	epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate, epicatechin
Panax ginseng	Saponin glycosides	Inhibits lipid peroxidation	Immunomodulator	Ginseng
Ginko biloba	Terpenoids	Improve its bioavailability	Incerebral insufficiency	Ginkgoflavoneglucoside Ginkgolides and Bilobalide, Ginkgoic acids

Table 2: Herbal EthosomeFormulations.[24-28]

Biological Source	Category	Application	Use	Active Ingredients
Glycyrrhiza glabra	Triterpenoid saponins glycosides	Improved Anti-inflammatory activity and sustained release action	Treatment of dermatitis, eczema and Psoriasis	Ammonium glycyrrhizinate
Cannabis sativa	Resins	Improved patient compliance and Increased skin permeation	Treatment of Rheumatoid arthritis	Tetrahydrocannabi-diol (THC)
Tripterygium wilfordii	Diterpene oxide	Increase in percutaneous permeability	Anti-inflammatory, Anti-tumour	Triptolide
Sophora alopecuerides	Quinazoline alkaloids	Increase in permeability	Anticancer, Antiendotoxic	Matrine, oxymatrine, sophoridine, sophocarpine (Alkaloidal extract)
Curcuma longa	Resins	Improved bioavailability	Anti-inflammatory	Curcumin

TRANSFERSOMES

The term and concept of Transfersome were introduced in 1991 by Gregor Cevc. The name means "carrying body", and is derived from the Latin word 'transferre', meaning 'to carry across', and the Greek word 'soma', for a 'body'. A Transfersome carrier is an artificial vesicle which resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery.[29]

Transfersome is a highly adaptable and stress-responsive, complex aggregate. It is an ultra-deformable vesicle which possesses an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimising. This enables the transfersome to cross various transport barriers efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents.[30]

These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency.[31] These vesicular transfersomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. Flexibility of transfersome membrane is achieved by mixing suitable surface-active components in the proper ratios.[32]

HERBAL TRANSDERMAL PATCHES

Transdermal drug delivery systems are self-contained discrete dosage form topically administered in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects.[37]

It has been found that drugs from herbal origin can be utilized with enhanced efficacy by incorporating in transdermal drug patches. Even herbal penetration enhancers like some terpenes are found to be potential enough to replace the conventionally available penetration enhancers like DMSO (Dimethyl Sulfoxide) which has several disadvantages.[38]

Herbal Transdermal patches are medicated adhesive pad designed to release active ingredients at a constant rate over a period of several hours or days after application to skin. Skin uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into blood stream.[39]

The first commercially available prescription patch was approved by the U.S. Food and Drug administration in December 1979, which administered scopolamine for motion sickness. The most common available transdermal drug delivery patches are the over-the-counter nicotine patches that help people quit smoking.[40]

Table 3: Herbal Transfersome Formulation.[33-36]

Biological source	Category	Application	Use	Active Ingredients
Capsicum annum	Resins	Increase skin penetration	Treatment of Rheumatism	Capsaicin
Curcuma longa	Resins	Increase skin permeability	Anti-inflammatory	Curcumin
Catharanthus roseus	Indole alkaloids	Increase in permeability	Anticancer	Vincristine
Colchicum automnale	Amino alkaloids	Reduction in GIT side effects	Treatment of Gout	Colchicine

Table 4: Marketed Herbal transdermal patches

Herbal Transdermal Patch	Active ingredients	Company	Use
Antismoking Patch –Nicoderm CQ	Nicotine	Glaxosmithkline	Quit smoking
Transdermal SCOP	Scopolamine	Novartis	Prevent motion sickness
Forest sap detox foot patch	Tourmaline, Chitosan, Pearl Stone, Wood vinegar	Natural Pharmacy	Detoxification, Increase oxygen intake
Slimming patch-Hoodia+ patch™	Hoodia Gordonni, Gaurana, *Garcinia combogia*	Medex patches	Weight control
Praan Painplast™	*Angelica dahuria, Rhizoma zingerbis, Chinese angelica*	Greatline Impex	Pain relief

NANOPARTICLES

Nanotechnology is science of matter and material that deal with the particle size in nanometers. The word "Nano" is derived from Latinword, which means dwarf ($1nm=10^{-9m}$).

Pharmaceutical nanotechnology embraces applications of Nano science to pharmacy as nanomaterial, and as devices like drug delivery, diagnostic, imaging and biosensor materials. Pharmaceutical nanotechnology has provided more fine-tuned diagnosis and focused treatment of disease at a molecular level. It helps in detecting the antigen associated with diseases such as cancer, diabetes mellitus, neuro-degenerative diseases as well as detecting the microorganisms and virus associated with infections.

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix.

Depending upon the method of preparation nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.[41]

Nanoparticles offer some specific advantages such as they help to increase the stability of drugs/proteins and possess useful controlled release properties. It can be modified to achieve both active and passive targeting; drug loading is very high and can be administered by various routes such as parenteral, nasal, intra ocular and oral routes.[42]

NANOEMULSIONS

Nanoemulsions are submicron sized emulsion that is under extensive investigation as drug carriers for improving the delivery of therapeutic agents. Nanoemulsion is a heterogeneous system and consist of two immiscible phase, one phase is oil phase other is aqueous phase, while the droplet is of submicron size range of 5-200nm.[54]

Nanoemulsions/Sub-micron emulsion (SMEs)/Mini-emulsions/Ultrafine emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 100 nm. Nanoemulsion, which is categorized as multiphase colloidal dispersion, is generally characterized by its stability and clarity. Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a co-surfactant or co-solvent is used in addition to the surfactant, the oil phase and the water phase.[55]

Nanoemulsions are made from surfactants approved for human consumption and common food substances that are "Generally Recognized as Safe" (GRAS) by the FDA.[56] There is an application of high shear generally obtained by micro fluid or ultrasonic approach generally used to reduce the droplet size to nanoscale.[57]

Since, the preparation of the first nanoemulsion in 1940s, it can be of three types such as oil-in-water (O/W), water-in-oil (W/O), and bicontinuous. The transformation between these three types can be achieved by varying the components of the emulsions.[58]

MICROEMULSION

The microemulsion concept was introduced in 1940 by Hoar and Schulman who generated a clear single-phase solution by titrating a formed milky emulsion with alcohol.[66]

In 1959, Schulman et al. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions".[67] Microemulsions is homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, usually in combination with a co-surfactant and whose diameter is in the range of 10-140 nm.[68]

Table 5: Herbal Nanoparticle Drug Delivery System.[43-53]

Biological Source	Category	Application	Use	Active Ingredient
Cuscuta chinesis	Flavonolignans	Improve water solubility	Antitumour, Immunostimulatory Antihepatotoxic	Ethanolic extracts
Glycyrrhiza glabra	Saponin glycosides	Improve the bioavailability	Anti-inflammatory, Anti-hepatotoxic, Antiviral	Glycyrrhizic acid
Tripterygium wilfordii	Diterpene oxide	Increase in solubility, Decrease in toxicity	Anti-inflammatory, Antitumour	Triptolide
Ginkgo biloba	flavonoids	Improved cerebral blood flow	Brain function activation	Extracts of Ginkobiloba
Naringenin	Flavonoids	Increase in solubility	Hepatoprotective	-
Artemisia annua	Alkaloid	Increase in therapeutic index	Anticancer	Paclitaxel
Berberis vulgaris	Isoquinoline alkaloid	Sustained drug release	Anticancer	Berberine
Camptotheca acuminata	Quinoline alkaloid	Increase in solubility	Increase in bioavailability, Antitumour	Hydroxy Camptothecin
Stephaniate trandria	Bisbenzylisoquino-line alkaloid	Sustained release action	Anti-inflammatory, Antiplatelet aggregation, Ca^{2+} channel block, immunosuppressive	Tetrandrine

Table 6: Herbal Nanoemulsion Formulations.[59-65]

Biological source	Category	Application	Uses	Active ingredients
Silibum marianum	flavonolignans	Increase in solubility and therapeutic activity	Hepato-protective	Silymarin
Berberis vulgaris	Isoquinoline alkaloids	Improve residence time and absorption	Anticancer	Berberine
Sophora alopencerides	Alkaloids	Increase in percutaneous permeability	Anti-bacterial, Anti-inflammatory, Anti-virus	Matrine
Curcuma zedoaria	Resins	Improved aqueous dispersibility, stability and oral bioavailability	Hepato-protection anticancer and anti-bacterial	β-elemene
Ubiquinone	Benzoquinone	Enhancement in solubility, bioavailability	Antioxidant	_
Colchicum autumnale	Indole alkaloid	Improved oral bioavailability	Treatment of gout	Colchicine
Genista tinctoria	*Isoflavones*	Improved skin permeation	Anticancer	genistein

Table 7: Herbal Microemulsion Formulations.[71-78]

Biological source	Category	Application	Use	Active ingredients
Ligusticum Wallichii	Alkaloids	Increased permeation rate	Inhibit platelet aggregation and Lower blood levels	Ligustrazine Phosphate
Tripterygium wilfordii	Diterpene oxide	Enhance the penetration by increase hydration	Anti-inflammatory	Triptolide
Taxus brevifolia	Diterpene	Improve residence time	Anticancer	Docetaxol
Quercetin	Flavonoids	Enhance penetration	Antioxidant	_
Azadirachitaindica	Tetranortriterpenoid	Low toxicity	Acricidal, Antifungal, Antibacterial	Neem oil
Pilocarpus Jaborandi	Amino Alkaloid	Improved ocular retention, Reduce systemic side effects	Treatment of Glaucoma	Pilocarpine
Radix puerariae	Tannins	Increase bioavailability	Cardio and cerebrovascular disease	Puerarin
Psoralea Corylifolia	Furocoumarin	Improved skin permeation	Treatment of psoriasis	Bavchi oil

They are promising delivery systems which allow sustained or controlled drug release for percutaneous, peroral, topical, transdermal, ocular and parenteral administration of medicaments. Enhanced absorption of drugs, modulation of the kinetics of the drug release and decreased toxicity are several advantages in the delivery process.[69]

Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating. Structurally, they are divided into oil-in-water (o/w), water in oil (w/o) and bicontinuous microemulsions. Recently, there has been a considerable interest for the microemulsion formulation, for the delivery of hydrophilic as well as lipophilic drug as drug carriers because of its improved drug solubilization capacity, long shelf life, ease of preparation and improvement of bioavailability. A microemulsion generally consists of four different components, a lipophilic phase, a hydrophilic phase, surfactant and co-surfactant.[70]

CONCLUSION

Extensive research is going on for herbal drugs to incorporate them in novel drug delivery systems. Application of these novel techniques to natural medicines will led to enhanced bioavailability, reduced toxicity, sustained release action, protection from GI degradation which cannot be obtained through conventional drug delivery system due to large molecular size, poor solubility, degradation of herbal medicines in GI media. Constituents like flavonoids, tannins, terpenoids, when incorporated into novel techniques showed enhanced bioactivity and targeted action at low therapeutic dose. Hence incorporation of herbal drugs into novel delivery techniques is also adopted on the industrial scale.

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