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Review Article

APPROACHES FOR IMPROVING THE PHARMACOLOGICAL AND PHARMACOKINETICS PROPERTIES OF HERBAL DRUGS

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Abstract: Despite the world wide adaptability of herbal plants and their products, these conventional drugs suffering with many pharmacological and pharmacokinetics constraints. Major drawbacks related with these traditional drugs includes low aqueous solubility and physical stability, reduce absorption, rapid metabolism, instability under high acidic conditions and inability to cross blood-brain barriers. The present review article discussed various novel drug delivery approaches (like Liposome, Emulsion, Transfersome, Ethosome and Microspheres) that are using to combat with these constraints. Various important issues related with natural drugs carrier like their generalized mode of action, their advantages over conventional drugs and methods of their preparation are summarized.

Key**words:** Herbal drugs, Novel Drug Delivery Approaches, Pharmacological Properties, Liposomes, Emulsion, Transfersome, Ethosome and Microspheres

Introduction

The herbal formulation, which is one of the major segments of traditional system of medicine, contributes immensely to the positive health of an individual. However, delivery of herbal drugs also requires modification with the purpose to achieve sustained release, to increase patient compliance etc.[1]. The efficacy of many herbal drugs is often limited by their potential to reach the site of therapeutic action. In most cases (conventional dosage forms), only a small amount of administered dose reaches to target site, while the majority of the drug distributes throughout the rest of the body in accordance with its physicochemical and biochemical properties such as low solubility, reduced absorption, rapid metabolism, instability in highly acidic pH conditions and excretion[2]. To minimize drug degradation, to reduce dose and its toxicity, increased solubility and stability and improved tissue macrophages distribution various drug delivery and novel drug delivery systems are currently under development[3-5]. Novel drug delivery system (NDDS) is advantageous in the delivering the herbal drug at predetermined rate and exhibits site specific action. In novel drug delivery technology, control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of drug at molecular level[6]. In phyto-formulation research, developing nano dosage forms like polymeric phyotosomes, nanoemulsion, ethosomes, pronisomes, floating drug delivery system, micro-emulsions have a number of advantages for herbal drugs, including enhancement of solubility, stability and bioavailability, protection from toxicity, enhancement of pharmacological activity, protection from physical and chemical degradation[1,5,7-9] Thus the NDDS have potential to address various problems related with herbal medicine practice (HMP).

The present review article was aimed to provide an overview of various novel drug delivery approaches utilized for modification of traditional herbal drugs, incorporating, botanical, active ingredient, biological activities of specific drug, factors affecting their efficiency, methods of preparation of such formulation and their potential advantages.

Liposomes

Honeywell-Nguyen and Bouwstra [10] were the first to studied liposome as an effective delivery system for the skin. Liposomes are lipid vesicles mainly composed of one or multiple lipid bi-layers composed of mixtures of phosphatidylcholines with long or short hydrocarbon chains. They have high morphological diversity as a function of hydration, temperature and composition [11]. A cross-section of liposome revealed the hydrophilic heads of the ampiphile orienting toward the water compartment while the lipophilic tails orient away from the water towards the center of the vesicle, thus forming a bilayer. Consequently, water soluble compounds are entrapped in the water compartment and lipid soluble compound aggregate in the lipid section. Liposome-based delivery system plays an important role owing to easy preparation, increasing the bioavailability, and also offers drug targeting and controlled release [12]. In addition, charged liposomes could be as carriers to enhance the permeation through the skin in the transdermal drug delivery which are administered by the percutaneous route [13]. Recently, it has been reported that liposomes had been employed in the field of plant polysaccharides and made encouraging successes. Liposomes possess unique physical and chemical properties, which not only improve polysaccharide stability, bioavailability, and difficulty in penetration to some cells but also enhance the pharmacodynamic action and induce the target [14].

This technique is efficiently utilize for enhancing the therapeutic index of anti-cancer agents, either by increasing the drug concentration in tumor cells and \or by decreasing the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon and by utilizing targeting strategies [15, 16] have summarized the role of liposome in liver related disorders. According to them liposomally delivered herbal drug could be taken up by Kuffer cells and provide protective effects in hepatocytes. Liposome provides following benefits enhance drug bioavailability, solubility and uptake, altered pharmacokinetics and bio-distribution and in vitro and in vivo stability and site specific action [1]. There is marked difference between phytosome and liposome; two basic differences are, in phytosome active chemical constituents molecules are anchored through chemical bonds to the polar head of the phospholipids whereas in liposome, the active principle is dissolved in the medium of the cavity or in the layers of the membrane. No chemical bonds are formed. In phytosome, phosphatidylcholine and the individual plant compound form a 1:1 or 2:1 complex depending on the substance, whereas in liposomes hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule. Various herbal liposomal formulations have been studied and they are summarized in Table 1. Essential oil from rhizome of *Atractylodes macrocephala* has been entrapped into liposomes by using rapid expansion supercritical solution technique (RESS). The essential oil of this plant were reported to treat various disorders related with gastro-intestinal tract and as anti-tumor. Incorporation of oil into liposomes improved the solubility and enhancing the bioavailability of this drug[17]. Hybrid liposomes of the silymarin extract were reported for buccal administration using cholesterol and stearyl amine for the treatment of liver disorders [37]. However, lower water solubility and poor gastrointestinal absorption limits its uses, liposomal formulation of this drug were prepared by using reverse evaporation technique where interaction between the silymarin and phospholipids led to increase permeation thereby increased bioavailability [18]. Film method and sonication technique were utilized for preparation of *Artemisia arborescen* liposome, this provide an increase stability and enhanced penetration into cytoplasmic barrier[19]. Extract of *Tripterygium wilfordi* has been incorporated into liposomes by thin film dispersion method, which led to increased stability at suitable temperature and reduced side effect [20]. Quercetin (*Sophora japonica*) required high dose for their antioxidant and anti-inflammatory activities and due to large molecular size of drug it cannot pass through from blood brain barrier. The liposomal formulation of this drug was developed by mixture of phosphtidylcholine, quercetin and dispersion in polyethylene glycol. This provides reduction in dose amount and side effect as well as better permeability thorough blood brain barrier [21]. Cosmetochem International AG a Swiss-based company, launched liposomal powders, named Liposome Herbasec® There are five extract in the current Liposome Herbasec® range which are standardized for specific phyto-chemicals. White and green tea are standardized for caffeine and total poly-phenols, white hibiscus for fruit acids, guarana for caffeine and *Aloe vera* is aloin-free product [7].

Emulsions

Emulsion is a biphasic system in which one phase in intimately dispersed in the other phase in the form of minute droplets. In emulsion, one phase is always water or aqueous phase, and the other phase is oily liquid, i.e. non-aqueous. Emulsion can be classified into ordinary emulsion (0.1-100 µm), micro-emulsion (10-100 µm) and sub-micro-emulsion (100-600 µm). Among them, the micro-emulsion is also called nano-emulsion and sub-micro-emulsion is also called lipid emulsion. Emulsion drug delivery system is targeted or distributed well due to affinity to lymph. Emulsion can release the drug for a long time because it is packed in the inner phase and makes direct contact with the body and other tissues. Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of hydrolyzed materials, improve the penetrability of drugs to the skin and mucous and reduce the drugs stimulus to tissues. The new type, viz., Elemenum emulsion, is uses as anti-cancer drug and safer for heart and liver. Emulsion formulation for various herbal bioactive have been reported and depicted in Table 2. Emulsion of *Taxus brevifolia* (Docetaxel), *Sophora japonica* (Quercetin) and *Tripterygium wilfordii* (Triptolide) were prepared by homogenization method that improves the bioavailability, absorption, penetration into stratum corneum and epidermis and sustained release of these drugs [22-25]. *Rheum rhabarbarumi* (Rhubarb) uses as laxative, anti-bacterial and anti-spasmodic, the conventional dose suffering from poor solubility and require high drug concentration for desired biological activity, the emulsion prepared by miceller electro-kinetic method provides better bioavailability and good penetration ability of rhubarb[26].

Transfersomes

Transfersomes are made up of phospholipids supplemented with single chain surfactant with a high radius of curvature which acts as edge activators to provide vesicle elasticity and deformability [27]. Transfersomes are specific deformable vesicles, which are being developed, considering the advantage of phospho-lipids vesicles, for suitable delivery of drug. These are highly elastic in nature; as such they could easily overcome the skin penetration, by squeezing themselves in a self-adapting manner. Also they possess a unique ability to get accommodated with a wide range of solubility and act as an efficient carrier for both low as well as high molecular weight drugs, e.g. analgesic, corticosteroids, hormones, anticancer drugs, insulin, proteins etc with high entrapment efficiency and a unique advantage of protection of the encapsulated drug, from metabolic degradation[28]. Transfersomes could be easily prepared using various processes - suspension homogenization process, aqueous lipid suspension process, modified handshaking process and centrifugation process. Transfersomes' inherent potential advantages are highly utilized in 'Transdermal Immunization', 'Peripheral Drug Targeting' & for 'Transdermal Delivery 'of Insulin, NSAIDs, Heparin, Anti Cancer drugs, etc. Transferosomes are applied in a non-occuledd method to the skin, which permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. It can be applicable as drug carriers for a range of small molecules, peptides,

protein and herbal ingredients[7]. Transferosomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting maintenance of skin [29]. Zheng et al [30] have evaluated influences of drug properties on the encapsulation efficiency and drug release of a transferosomes. According to them high molecular weight and opposite charges to the membrane may provide transferosomes with high encapsulation efficiency. Capsaicin transferosomes were prepared by the high shear dispersion technique and the penetration of capsaicin transferosomes was found to be more resulting better topical absorption as compared to pure drug[31] Table 3. Colchicines and Curcumin transferosomes were prepared using hand shaking method, these formulation prevent drugs from gastro-intestinal side effect associated with oral administration and provide local, sustained and site specific delivery of colchicines and Curcumin [32,33]. Transferosomes of vincristine were prepared by using lecithin and sodium deoxycholate in 70/20 ration. This formulation increases the entrapment efficiency and improved skin penetration [34].

Ethosomes

Ethosome are soft, malleable lipid vesicles composed mainly of phospholipids, alchol (ethanol or isopropyl) in relatively high concentration (20-45%) and water [35]. Ethosomes are novel lipid carriers and can be tailored for enhanced skin delivery. Ethosome, as a novel liposome, is especially suitable as a topical or trans-dermal administration carrier [36]. It has a high deformability and entrapment efficiency and can penetrate through the skin. Compared to other liposome, the physical and chemical properties of ethosomes make the delivery of the drug through the stratum corneum into a deeper skin layer efficiently or even into the blood circulation [37]. This property is very important as the topical drug carrier and trans-dermal delivery system. Moreover, the ethosomes carrier also provide an efficient intercellular delivery for both hydrophilic and lipophilic drugs. Ethosome are platform for the delivery of large amount of diverse group of drug and these drug is administrated in semi solid form resulting in improved patient compliance [38]. Ethosome suspension of ammonium glycyrrhizinate (Table 4) was prepared (by solvent depression method) for the dermal administration. The glycyrrhiznic ethosome increase in-vitro precutaneos permeation and significantly enhance its anti inflammatory activity [39]. Ethosome of *Tripterygium wilfordi* (Triptolide) were prepared by controlling filming rehydration and ultrasonic method and evaluated in the rat model for erythma. This ethomal formulation showed an increase in precutaneous permeability, high entrapment efficiency compared to their traditional formulation [40]. Ethosmoe of *Sesbania grandifolia* were developed by solvent dispersion method that enhance it trans-dermal permeation. Similarly ethosome of alkaloid of *Sephora alopecuroides* were prepared by transmembrane pH active loading methods that enhance drug delivery and stability.

Microspheres

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm [41]. As a delivery system microspheres are advantageous because they can ingested or injected and: they can be tailored for desired release profiles and used site-specific delivery of drug and in some cases can even provide organ-targeted release [7]. A number of plant ingredient have been micro-capsulated for various application (Table 5). Microsphere of *Curcuma longa* oleoresin were prepared through emulsion solvent diffusion method and this formulation supports sustained drug release [42]. Micro-encapsulation of Zeodary turmeric oil into microsphers via quasi-emulsion solvent diffusion has been used for bioavailability enhancement and sustained drug release [43].

Oxidised cellulose microsphere containing *Camphtotecha acuminate* were prepared by using evaporation method, has been successfully use for prolonged release of camptothecin drug. Similarly microsphere of *sophora japonica* (Quercetin) has been prepared by solvent evaporation method that significantly decreases the drug molecular size and this novel drug can easily pass through from blood barrier [44].

Table 1. Herbal Liposome Formulation

Botanical	Formulation	Biological activity	Active Ingredient	Drawback of traditional dose	Application of Liposomal formulation	Method of preparation
Atractylodes macrocephala	Essential of *A. macrocephala*	Anti-tumor and use in various gastro-intestinal diseases	Essential oil and their oxide derivatives	Lower solubility and bioavailability	Improved solubility and enhancing bioavailability	Rapid expansion of supercritical solution (RESS) technique [17]
Tripterygium wilfordi	Triptolide	Anti-inflammatory	Diterpene triepoxide	Poor water solubility and toxicity	Increase stability and reduce side effects	Thin film depression method [20]
Sophora japonica	Quercetin	Antioxidant and anti-inflammatory and anti-cancer	Quercetin, 3,3′,4′,5′-7-pentahydroxy flavones	Required high dose, due to high particle size it cannot pass	Reduced dose, and side effect, enhance penetration in blood brain barrier, and bioavailability	By using mixture of egg phosphotidylcholine, quercetin and dispersion in polyethylene glycol [21]

				through from blood brain barrier		
Silybum marianum	Silymarin extract	Hepatoprotective antioxidant for liver and skin	Silibinin (Flavonoids)	Low water solubility and poor absorption in gastrointestinal tract	Interaction between silymarin and phospholipids led to increased permeation thereby increased bioavailability	Reverse evaporation technique [18]
Artemisia arborescen	Artemisia	Antiviral	Artemisine	Low stability and penetrability	Increase stability, anti-herpetic activity, enhance penetration into cytoplasmatic barrier	Film method and sonication technique [19]
Capsicum annua	Capsaicin liposome		Capsaicin	Lower penetrability and stability	Increase in skin permeation as well as prolongation of duration of action	Reverse evaporation technique [45]
Magnolia officinalis	Magnolol liposome	Anti-oxidant, Inhibiting vascular smooth muscle cells proliferation	Honokiol and Magnolol phenols	Lower therapeutic and stability	Enhance therapeutic efficiency	Magnolol and phospholipid mixed by ultrasonic facilitation [46]
Strchnos nux-vomica	Nux vomica limpsome	Anti-tumor, Analgesic	Alkaloid	Low stability	High encapsulation efficiency improved stability in blood, and relative low price of phospholipids of the novel liposomes	liposomes composed of hydrogenated soybean phosphatidylcholine (HSPC) and soybean phosphatidylcholine (SPC) containing the total alkaloids from seed of Strychnos nux-vomica [47]
Diospyros montana	Diospyrin liposome	Anti-bacterial and anti-tumor	Bis-napthoquinone	Low water solubility, toxicity	Enhancement of its anti-tumor effect	Reveres evaporation technique [48]
Myrtus cummunis	Myrtle liposome	Anti-bacterial and anti-oxidant	Myrtle oil that includes myretnol, myrtenol acetate, limonene, linalool and alpha pinene	Less solubility	Increase its activity	Thin film method [49]
Radix puerariae	Puerarin	Cardio-protective and anti-arrhythmia activity	Isoflavoinoid	Low water solubility	Modify their surface charge and membrane integrity	Film depression ultrasonic method [50]
Ampelopsis grossedntata	Ampelopsin	Anti-cancer and anti-oxidant	Ampelopsin	Lower bioavailability	Increase efficiency	Film ultrasound method [51]
Taxus brevifolia	Paclitaxel	Anti-tumor	Paclitaxel	Poor water solubility	High entrapment efficiency (94%)	Thin film hydration method [52]
Curcuma longa	Curcumin Liposome	Antioxidant and anti-cancer	Curcumin or diferuloylmethane	Low bioavailability	Long circulating with high entrapment	Ethanol injection method [53]

			(yellow polyphenol)		efficiency	
Allium sativum	Garlicin liposome	Anti-oxidant	Flavanoid and diallylsulfide and trisulfide	Low water solubility	Increase efficiency	Revers-phase evaporation method [54]
Cladonia substellata	Usnic acid with β-cyclodextrin	Anti-mycobaterial	Usnic acid, 2,6-diacetyl-7,9-dihydroxy-8, 9b-dimetyl-1,3(2H,9bH)-dibenzeno-furandione	Lower solubility	Increased solubility and localization with prolonged release profile	Hydration of a thin lipid film method with sonication [55]
Scutellaria baicalensis	Wogonn liposome	Anti-xylotic and Anti-cancer	O-methylated flavones	Low Stability	Sustained release effect	Film dispersion method [56]
Colchicum autumnale	Colchicine liposome	Antigout	Colchicine	Poor bioavailability due to gastro-intestinal side effects	Enhance skin accumulation, prolong drug release and improve site specificity	Rotary evaporation sonication method 5[7]
Thea chinensis	Catechins Liposome	Anti-oxidant and chemopreventive	Catechins	Poor penetration	Increase permeation through skin	Rotary evaporation sonication method [58]
Erigeron breviscapus	Breviscapie liposome	Cardio-protective	Scutellarin (4′, 5, 6-tetrahydroxy flavone- 7-*O*-glucuronide	Poor water solubility	Sustained drug delivery	Double emulsification process [59]

Table 2. Herbal Emulsion Formulation

Botanical	Formulation	Biological activity	Active Ingredient	Drawback of traditional dose	Application of emulsion formulation	Method of preparation
Taxus brevifolia	Docetaxel	Anti-neoplastic agent, anti-cancer, cely cycle specific drug	Docetaxel	Lower bioavailability (8-9%) and absorption	Enhance bioavailability, improve solubilisation ability of hydrophilic drug and improve residence time	High pressure homogenization method [22]
Sophora japonica	Quercetin	Antioxidant and anti-inflammatory	Quercetin, 3,3′,4′,5′-7-pentahydroxy flavones	Poor bioavailability	Enhance penetration into stratum corneum and epidermis	Homogenization method [23]
Tripterygium wilfordii	Triptolide micro-emulsion	Anti-inflammatory	Diterpene triepoxide	Poor water solubility and toxicity	Enhance the penetration of drugs through the stratum corneum by increase hydration	High pressure homogenization method [24,25]

Rheum rhabarbarum	Rhubarb	Laxative, Antibacterial, Haemostatic and antispasmodic	Anthraquinones and bianthrones	Poor solubility, high drug concentration	Enhance bioavailability and penetration ability	Miceller electrokinetic chromatography [26]
Azadirachta indica	Neem oil	Anti-malarial, anti-fertility and anti-fungal	Azadiratine	Poor solubility and stability	Enhance stability and its acaricidal activity	Tween-80 and Sodium dodecyl benzene sulfonate (SDBS) were used as compound surfactants [60]
Berberis vlulgaris	Berberine	Anti-neoplastic activity,	isoquinoline alkaloids	Poor bioavailability and absorption	Improve residence time and absorption	Drawing ternary phase diagram [611]
silybum marianum	Silybin	Hepatoprotective	Flavonoid silymerine	Lower dissolution rate	Sustained release formulation	Emulsification method [62]
Curcuma longa	Zedoary turmeric oil	Hepatoprotective, anticancer and antibacterial	Curcumin	Poor aqueous solubility and stability	Improved aqueous solubility, stability and oral bioavailability	Drawing ternary phase [63]

Table 3. Herbal Transferosomes Formulation

Botanical	Formulation	Biological activity	Active Ingredient	Drawback of traditional dose	Application of emulsion formulation	Method of preparation
Capsicum annua	Capsaicin	Analgesic	Capsaicin		Increase skin penetration	High Shear dispersion Method [31]
Colchicum autumnale	Colchicines	Antigout, leuko-cytoclastic vasculitis, psoriasis, and Sweet's syndrome	Colchicines	Gastrointestinal side effects and its accumulation in the body leads to bone marrow suppression	Increase skin penetration	Hand Shaking Method [32]
Curcuma longa	Curcumin	Manage Osteoarthritis, Uveitis and chronic eye inflammation and diabetic angiopathy	Curcumin or diferuloylmethane (yellow polyphenol)	Low bioavailability due to lower absorption in gastro-intestinal tract	Increase in permeation	hand shaking method using surfactant [33]
Catharanthus rosesus	Vincristine	Anti-cancer, Lymphoma, Leukemia	Vincristine, Catharnthine, Vindoline alkaloid		Increase entrapment efficiency and skin penetration by improving the pre-cutaneous permeation	By using lecithin and sodium deoxycholate in 70/20 ratio [34]

Table 4. Herbal Ethosome Formulation

Botanical	Formulation	Biological activity	Active Ingredient	Drawback of traditional dose	Application of ethosome formulation	Method of preparation
Glycyrrhiza glabra	Amonium glycyrrhizinate ethosome	Anti-inflammatory	Glycrrhizic acid	Poor permeability	Increases of in vitro percutaneous permeation and significantly enhanced anti-	solvent dispersion method [39]

					inflammatory activity	
Tripterygium wilfordi	Triptolide	Anti-inflammatory	Diterpene triepoxide	Poor water solubility and toxicity	high entrapment efficiency, good percutaneous permeability	combining filming-rehydration method ultrasonic method [40]
Podophyllum hexandrum	Podophyllotoxin	Purgative, anti-rheumatic, antiviral and antitumor	Etoposide and Teniposide	Slow pharmacological action	Higher entrapment efficiency and enhance its therapeutic effect	solvent dispersion method [64]
Sesbania grandiflora	Sesbania ethosome	Anti-miocrbial	leucocyanidin and cyanidin	Poor permeability	Enhance Trans-dermal permeation	solvent dispersion method [65]
Sophora alopecuroides	Sophora ethosome	Antiendotoxic, anticancer, and anti-inflammatory	Sophocarpine, matrine, oxymatrine, sophoridine,	low percutaneous penetration and bitter taste	Enhance drug deliver and stability	transmembrane pH gradient active loading method [66]
Sophora flavescens	Matrine ethosome	Cardio-protective, Anti-inflammatory	Matrine and oxymatrine alkaloid	Lower bioavailability	Improve precutaneous permeation	Solvent dispersion method [67]

Table 5. Herbal Microspheres Formulation

Botanical	Formulation	Biological activity	Active Ingredient	Drawback of traditional dose	Application of ethosome formulation	Method of preparation
Curcuma longa	Curcumin floating microspheres	Antioxidant, anti-arthritic and anti-cancer	Curcumin or diferuloylmethane (yellow polyphenol)	Low bioavailability	Sustained drug release	Emulsion solvent diffusion method[42]
Curcuma longa	Zeodoary oil microsphere	Hepatoprotective, anti-arthritic and anti-cancer	Curcumin or diferuloylmethane (yellow polyphenol)	Low bioavailability	Sustained release and higher bioavailability	Quasi-emulsion-solvent diffusion method [43]
Sophora japonica	Quercetin	Antioxidant and anti-inflammatory and anti-cancer	Quercetin, 3,3′,4′,5′-7-pentahydroxy flavones	Required high dose, due to high particle size it cannot pass through from blood brain barrier	Significantly decrease the dose size	Solvent evaporation [44]
Ruta gravelons	Rutin-alginate-chitosan-micerocapsules	Useful for Cadriovascular and cerbrovascular diseases	Flavonoid	Unspecific site of action	Targeting into cardio-vascular and cerbro-vascular region	Complex coacervation method [68]
Camptotehca acuminate	CPT loaded microsphere	Anti-cancer	Camptothecin (CPT) is a cytotoxic quinoline alkaloid	Poor aqueous solubility and stability	Prolonged release of camptothecin	Oil in water evaporation method [69]

Conclusion

The interdisciplinary nature of NDDS technology enables diversification and development in order to improve quality of life. 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 and so on. With the advancement of standardization, extraction,

identification techniques scientists now able to focuses their research for development of herbal drugs that can suit with modern system of medicine with targeted delivery, lesser amount and side effects properties. In present review it was immerged that large molecular size, lower water and lipid solubility, degradation of drug in gastro-intestinal tract, high dose requirement, slow pharmacokinetics, and toxicity problems restricted the in-vivo therapeutic activities of herbal drugs. Standardized plant extracts or mainly polar phyto-constituents like terpenoids, tannins, flavonoids when administered through novel drug delivery system show much better absorption better absorption profile which enables them to cross the biological membrane, resulting enhanced bioavailability. Hence novel drug delivery systems having a great potential to develop a site specific drugs.

Future Challenges

Beside the many advantage of these drug delivery approahces, still there are many technological challenges in developing the following techniques:

1.Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways.
2.Controllable release profiles, especially in case of sensitive drugs.
3.Materials for such NDDS those are biocompatible and biodegradable.
4.Architectures/ structures, such as biomimetic polymers, nanotubes, etc.
5.Technologies for self-assembly;
6.Functional improvement (active drug targeting, on-command delivery, intelligent drug release devices/bio-responsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery)
7.Improve devices such as implantable devices/nanochips for nanoparticle release, or Multi-reservoir drug delivery-chips.

To overcome these gaps the steps are needed to a) identify and isolate phyto-constituents which are compatible with various NDDS techniques, b) develop highly efficient and low cost NNDS techniques, c) formulate universal formulation schemes that can be used as intravenous, intramuscular or peroral drugs, d) develop better disease markers in terms of sensitivity and specificity, e) generate cell and gene targeting systems, f) device combined therapy and medical imaging, for example, nanoparticles for diagnosis and manipulation during surgery (e.g. thermotherapy with magnetic particles) and g) develop devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic nanoparticles that can correlate with the amount of ligand.

References

1 Goyal A, Kumar M, Nagpa M, Singh I, Arora S. "Potential of Novel drug delivery system for herbal drugs". *IJPER*, **2011**, 45, 225-335.

2 Tiyaboonchai W, Tungpradit W, Plianbangchang P. "Formulation and characterization of curcuminoids loaded solid lipid nano-particles". *Int J Pharm*, **2007**, 337, 299–306.

3 Charman, WN, Chan, HK, Finnin BC. "Drug delivery, a key factor in realizing the full therapeutic potential of drugs". *Drug Dev Res*, **1999**, 46, 316-327.

4 Mukherjee PK, Venkatesh P, Vankathesh M, Ponnusankar S, and Yaseen K. "Strategies for revitalization of traditional medicine". CHM, **2010**, 2 (11),1-15

5 Kumar K, Rai AK. "Miraculous therapeutic effects of herbal drugs using novel drug delivery system". *IRJP*, **2012**, 3, 27-30.

6 Atmzkuri LR, Dathi I. "Current trends in herbal medicines". *J Pharma Sci*, **2010**, 3 (1), 109-113.

7 Saraf AS. "Application of novel drug delivery system for herbal formulation". *Fitoterapia*, **2010**, 81, 680-689.

8 Thakur L, Ghodasra U, Patel N, Dabhi M. "Novel approaches for stability improvement in natural medicines". *Pharmacognosy Rev*, **2011**, 5, 48-54.

9 Yadev D, Suri S, Choudhary AA, Sikender M, Heman, Beg MN. "Novel approach, herbal remedies and natural products in pharmaceutical science as nano drug delivery systems". *IJPT*, **2011**, 3, 3092-3116.

10 Honeywell-Nguyen PL, Bouwstra JA. "Vesicles as a tool for transdermal and dermal delivery". *Drug Disc Today Technol* **2005**, 2,67–74.

11 Barbosa-Barros L, Barba C, Rodríguez G, Cócera M, Coderch L, López-Iglesias C, de la Maza A, López O. "Lipid nanostructures, Self-assembly and effect on skin properties". *Mol Pharm* **2009**, 6,1237–1245.

12 Rodriguez MLG, Rabasco AM. "Charged liposomes as carriers to enhance the permeation through the skin". *Expert Opinion on Drug Delivery* **2011**, 8, 857–871.

13 Chen M, Zhou Y, Huang J, Zhu P, Peng X, Wang Y. "Liposome based delivery systems in plant polysaccharides". *Journal of Nanomater*, **2012**, 1-4

14 Zuozhen F, Dongxiu G, Xiaoting Z. "Study on the preparation process of the *Codyceps sinensis* Sacc polysaccharide liposomal oral liquid by orthogonal design". *China Pharmaceuticals*, **2005**. 14, 50–51.

15 Sharma G, Snsnoudi S, Ehrhardt C, Kumar MNVR. "Liposome as targated drug delivery system". Journal Drug Targeting, **2006,** 14: 301-310.

16 Kashaw V, Nema AK, Agarwal A. "Hepatroprotective prospective of herbal drug and their vesicular carriers- a review". *Inter J Res Pharma Biomedi Sci*, **2011**, 2 (2), 360-374.

17 Wen Z, Liu B, Zheng Z, You X, Pu Y, Li Q. "Preparation of liposomes entrapping essential oil from *Atractylodes macrocephala* by modified RESS technique". *Chem Eng Res Design*. **2010**, 88 (8A), 1102-1107.

18 Mohamed S, El-Samaligy, Nagia NA, Mahmoud EA. "Evaluation of hybrid liposomes-encapsulated silymarin regarding physical stability and in vivo performance. *Int J Pharm",* **2006**, 319, 121-129.

19 Chiara S, Alessandro DL, Francesso L, Donatella V, aria M, Giuseppe L. "Liposomal incorporation of *Artemisia arborescens* essential oil and in vitro antiviral activity". *Eur J Pharm Biopharm* **2005**, 59, 161-169.

20 Li HR, Li SF, Duan HQ. "Preparation of liposomes containing extract of *Tripterygium wilfordii* and evaluation of its stability". *Zhongguo Zhong Yao Za Zhi*. **2007**, 32 (20), 2128-2131.

21 Priprem A, Watanatorn, J, Sutthiparinyanont S, Phachonpai W and Muchimapura S. "Anxiety and cognitive effect of Quercetin liposomes in rats". *Nanomedicine* **2008**, 4, 70-78.

22 Yin Y, Cui FD, Chung S. "Docetaxel microemulsion for enhanced bioavaila"bility, preparation and *in vitro* and *in vivo* evaluation". *J Control Release* **2009**, 140, 86-94.

23 Rogerio AP, Dora CL, Andrade EL, Chaves JS, Silva LFC, Senna EL, Calixlo JB. "Anti-inflammatory effect of querctin loaded microemulsion in the airways allergic inflammatory model in mice". *Pharmacol Res.* **2010**, 61 (4), 288-297.

24 Chen H, Chang X, Zhao X, Gao Z, Yang Y, Xu H, Yang X. "A study of micro emulsion system for transdermal delivery of triptolids". *J Control Release*. **2004**, 98 (3), 427-436.

25 Guan Y, Yan Z, Chen L, Zhu W, Yang M. "Pharmacokinetics of triptolids in *Triptergium wilfordii* microemulsion gel". *Znongguo Znong Yao Za Zhi*. **2011**, 36 (2), 216-219.

26 Sun SW, Yeh PC. "Analysis of rhubarb anthraquinones and bianthones by microemulsion electrokinetic chromatography". *J Pharma Biomed Ana* **2005**, 36, 995-1001.

27 Cevc G, Blume G, Schatzlein A, Gebauer D, Paul A. "The skin, A pathway for systemic treatment with patches and lipid-based agent carriers". *Adv Drug Deliv Rev*. **1996**, 18,349–378.

28 Prajapati ST, Patel CG, Patel CN. "Transfersomes, a vesicular carrier system for transdermal drug delivery". *AJBPR*. **2011**, 2 (1), 507-524.

29 Benson HAE. "Transfersomes for transdermal drug delivery". *Opin. Drug Deliv* **2006**, 3 (6), 727-737.

30 Zheng Y, Hou SX, Chen T, Lu Y. "Preparation and characterization of transfersomes of three drugs in vitro". *China Journal of Chinese material Medical*. **2006**, 31 (9), 728-731.

31 Long XY, Luo JB, Lin D, Rong HS, Huang WM. "Preparation and in vitro evaluations of topically applied capsaicin transfersomes". *Zhonggu Zhong Yao Za Zhi* **2006**, 31(12),981-984.

32 Singh HP, Utreja P, Tiwary AK, Jain S. "Elastic liposomal formulation for sustained delivery of colchicine, in vitro characterization and in vivo evaluation of anti-gout activity". *AAPS J* **2009**, 11 (1), 54-64.

33 Patel R, Singh SK, Singh S, Sheth NR, Gendle R. "Development and characterization of curcumin loaded transferosomes for trasnsdermal delivery". *J Phar Science*. **2009**, 1 (4), 71-80.

34 Lu Y, Hou SX, Zhang LK, Li Y, He JY, Guo DD. "Transdermal and lymph targeting transfersomes of vincristine". *Yao Xue Xue Bao* **2007**, 42 (10), 1097-1011

35 Rakesh R, Anoop KR, "Ethosome for transdermal and topical drug delivery". *IJPPS* **2012**, 4 (3), 17-24.

36 Shah MB, Shah AJ, Shah R. "An overview of ethosome as advanced herbal drug delivery system". *IJRRPAS* **2012**, 1, 1-14

37 Dayan N, Touitou E. "Carriers for skin delivery of trihexyphenidyl HCl, ethosomes vs. Liposomes". *Biomaterials*. **2000**, 21, 1879-1885

38 Chaturvedi M, Kumar M, Singhal A, Saifi A. "Recent development in novel drug delvery system for herbal drugs". Inter J Green Pharm **2011**, 5, 87-94.

39 Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M. "Ethosomes for skin delivery of ammonium glycyrrhizinate, *In vitro* percutaneous permeation through human skin and *in vivo* anti-inflammatory activity on human volunteers". *J Control Release*. **2005**, 106, 99–110

40 Chen JG, Jiang Y, Yang ZB. "Preparation of triptolide ethosomes". *AJPP* **2012**, 6(13), 998-1004

41 Singh P, Prakash D, Ramesh B, Singh N, Mani TT. "Biodegradable Polymeric Microspheres as Drug Carriers, A Review". *Indian Journal of Novel Drug Delivery* **2011**, 3 (2), 70-82.

42 Kumar K, Rai AK, "Evaluation of ant-inflammatory and anti-arthritic activities of floating microsphere of herbal drug". *IRJP* **2012**, 3 (1), 186-193.

43 Chen M, Wang S, Tan M, Wang Y. "Applications of Nano-particles in Herbal Medicine, Zedoary Turmeric Oil and Its Active Compound β-Elemene". *Am J Chin. Med* **2011**, 39, 1093-1098

44 Chao P, deshmukh M, Kutscher HL, Gao D, Rajan SS, Hu P, Laskin DL, Stein S, Sinko PJ. "Pulmonary targeting micro-particulate camptothecin delivery system, anticancer evaluation in a rat orthotropic lung cancer model". *Anticancer Drugs* **2010**. 21 (1), 65-76.

45 Mahajan A, Mangat P, Bhatia A, Katar OP. "A novel herbal capsaicin loaded liposomal formulation, design, development end evaluation". *Pharmaceut Sci* **2010**, 1-11,

46 Chen CYC, Wu CH, "Magnolol encapsulated by liposome in smooth muscell cell proliferation". *Journal of the Chinese society*, **2008**, 55, 517-521.

47 Chen J, Zhang T, Cai B, Chen M, Fang Y. "Pharmaceutical properties of novel liposomes containing total alkaloids from seed of Strychnos nux-vomica". *Zhongguo Zhong Yao Za Zhi* **2010**,35(1),35-9

48 Hazra B, Kumar B, Biswas S, Pandey BN, Mishra KP. "Enhancement of the tumor inhibitory activity, *in vivo* of diospyrin, a plant derived quinonoid through liposomal encapsulation". *Toxical Lett*. **2005**, 157, 109-117.

49 Gortzi O, Lalas S, Chinou L. "Reevaluation of bioactivity and antioxidant activity of *myrtus communis* extract before and after encapsulation in liposome". *Eur Food Res Tech*, **2008**, 226, 583-590.

50 Rong G, JuQun X. "Studies on molecular interaction between puerarin and PC liposomes". *Chinese Science Bulletin*. **2007**, 52, 2612-2617.

51 He ZF, Liu DY, Zeng S, Ye JT. "Study on preparation of ampelopsin liposomes". *Zhongguo Zhong Yao Za Zhi* **2008**, 33 (1), 27-30.

52 Kan P, Tsao CW, Wang Aj, Su CW, Liang Fh "A Liposomal Formulation Able to Incorporate a High Content of Paclitaxel and Exert Promising Anticancer Effect". *J Drug Delivery*. **2011**, 1-9

53 Dhule SS, Penfornis P, Frazier T, Walker R, Feldman J, Tan G, He J, Alb A, John V, "Pochampally R. Curcumin-loaded γ-cyclodextrin liposomal nano-particles as delivery vehicles for osteosarcoma". *Nanomedicine* **2012**, 8 (4), 440-451

54 Khan A, Shukla Y, Kalra N, Alam M, Ahmad MG, Hakim SR, Owais M. "Potential of Diallyl Sulfide Bearing pH-Sensitive Liposomes in Chemoprevention Against DMBA-Induced Skin Papilloma". *Mol Med* **2007**, 13 (7-8), 443-451.

55 Lira MCB, Ferraz MS, deSilva DGVC, Cortes MEC, Teixeira KI, Caetano NP, Sinisterra RD, Ponchel G, Magalhaes NSSS. "Inclusion complex of usnic acid with beta cycldextrin, characterization and nano-capsulation into liposomes". *J Incl Phenom Macro Chem* **2009**, 64 (3-4), 215-224

56 Xue KE, Yng XU, Fei Y, Neng PQ. "Preparation of wogonin liposomes and its pharmacokinetics in rat"s. *Journal of China Pharmaceutical University*. **2007**, 6, 502-506

57 Criellard BJ, Wal CD, Le HT, Bode AT, Lammers T, Hennink WE. "Liposomes as carriers for colchicines derived pro-drugs, vascular disrupting nano-medicnes with tailorable drug release kinetics". *Eur J Pharm Sci*, **2012**, 45 (4), 429-435.

58 Fang JY, Lee WR, Shen SC, Huang YL. "Effect of liposome encapsulation of tea catechins on their accumulation in basal cell carcinomas". *J Dermatol Sci* **2006**, 42(2), 1-6

59 Zhong H, Deng Y, Wang X, Yang B. "Multi-vesicular liposome formulation for the sustained delivery of breviscapine". *Int J Pharm*. **2005, 12**, 15-24.

60 Xu J, Fan QJ, Yin ZQ, Li XT, Du YH, Jia RY. "The preparation of neemoilmicroemulsion (*Azadirachta indica*) and the comparison of acaricidal time between neemoilmicroemulsion and other formulations in vitro". *Veterinary Parasitology*. **2010**, 3-4, 399-403

61 Wu SH, Ging WO. "Preparation, quality and safety evaluation of *berberine* nanoemulson for oral application". *Journal of Shanghai Jiatonog University (Agricultural Science).* **2007**, 1, 60-65

62 Song YM, Ping QN, Wu ZH. "Preparation of silybin nanoemulsion and its pharmacokines in rabbits". *Journal of china Pharmaceutical University* **2005**, 5, 427-431.

63 Zhao Yi, Wang C, Alber HL, Chow KR, Gong T, Zhang Z, Zheng Y. "Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil, Formulation and bioavailability studies". *Pharmaceutical Nanotechnology*, **2010**, 383, 170-177.

64 Yan-Yan Y, Hui ZJ, Ping FN, Ting WH, Tai ZY. "Entrapment efficiency of podophyllotoxin-encapsulated ethosome by minicolumn centrifugation-HPLC". *Chinese Traditional and Herbal Drugs***, 2010**, 10, 12-17

65 Nirved U, Lokesh V, Prasad MG, Joshi HM. "Formulation and evaluation of ethosomes of Sesbania grandiflora Linn. Seeds. Novel Science". *Inter J Pharmaceutical Sci*, **2012**, 1(6), 274-275

66 Zhou Y, Wei, Y, Liu H, Zhang G, Wu, X. "Preparation and In vitro Evaluation of Ethosomal Total Alkaloids of *Sophora alopecuroides* Loaded by a Transmembrane pH-Gradient Method". *AAPS PharmSciTech*, **2010**, 11 (3), 1350-1358

67 Zhaowu Z, Xiaoli w, Yangde Z, Nianfeng. "Preparation of matrine ethosome, its percutaneous permeation in vitro and anti-inflammatory activity in vivo in rats". *J Liposome Re*. **2009**, 19 (2), 155-162.

68 Xiao XH, Liu FQ, Shi CH, Li LY, Qin SY, Qiao CZ, Su ZW. "RAPD polymorphism and authentication of medicinal plants from Turmeric (*Curcuma* L.) in China." *Chi Trad. Herb Drugs*, **2000**, 31, 209-212.

69 Machida Y, Onishi H, Kurita A, Hata H, Morikawa A, Machida Y. "Pharmacokinetics of prolonged release CPT 11 loaded microspheres in rats" *J Control Release* **2011**, 39, 1093-1099