



## **Novel Approaches of Herbal Drug Delivery**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author SA carried out the review study and wrote the first draft of the manuscript. Authors IJ and AHMNH were involved in checking of reference and citation of the article. Author KND designed the study, wrote the final manuscript and revised the manuscripts according to expert opinions. All authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2018/39143

#### Editor(s):

(1) Jinyong Peng, Professor, College of Pharmacy, Dalian Medical University, Dalian, China.

#### Reviewers:

(1) Anna Gumieniczek, Medical University of Lublin, Poland.

(2) Syed Umer Jan, University of Balochistan, Pakistan.

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(4) Patil Sachinkumar Vasantrao, Shree Santkrupa College of Pharmacy, India.

(5) Bonglee Kim, College of Korean Medicine, Kyung Hee University, South Korea.

Complete Peer review History: <http://www.sciencedomain.org/review-history/23772>

**Review Article**

**Received 31<sup>st</sup> December 2017**

**Accepted 9<sup>th</sup> March 2018**

**Published 22<sup>nd</sup> March 2018**

### **ABSTRACT**

From ancient times, herbal medicines are in use to cure the diseases due to their potential and less side effects. But difficulties in identification, processing, standardizing, extracting of herbal drugs, it rarely attracts scientists towards the development of novel delivery systems for herbal drugs. The reduced efficacy of herbal drugs is due to the traditional and out of date approach of administration to patients. 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. Novel approach of delivering herbal drugs will increase the efficacy and safety of herbal medicines along with the increased stability of the drug product. These techniques provide improved patient compliance, sustained release and targeted action of plant actives and extracts. This review summarizes the information of various novel techniques used for improving safety and efficacy of phytomedicines, type of active ingredients, biological activity and application of novel formulation of herbal drugs to achieve better therapeutic response.

**Keywords:** Herbal drug; novel drug delivery system; natural products.

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## 1. INTRODUCTION

In recent years, scientists are extensively involved in the research and development of novel approach of delivering herbal drugs [1]. Natural products isolated from the plants are known as 'herbal drugs' and are the core of traditional medicinal systems that are being followed from ancient times [2]. With the progress of science and technology in the field of formulation technology of drug products, now a day's herbal dosage forms have evolved from simple mixtures and pills to highly sophisticated technology-based drug delivery systems [3]. In ancient time 90-95% drug materials were from natural sources. Information on the source of drugs indicates that half of the drugs that are employed today are based on natural products. In today's world, herbal drugs are getting more popularity to cure diseases with less toxicity and better therapeutic outcome. Incorporation of sophisticated technology in delivering herbal or plant based products increased drug product stability, reduces pre systemic metabolism and toxic effects by accumulation of drugs to the non targeted areas and also increase patient compliance due to ease in drug administration and acceptability [4]. The complexity of active constituents makes it very challenging to the development of novel drug delivery system for herbal products [5]. Hence, for enhancing the bioavailability of the drugs, there should be novel drug delivery systems and those can protect the drug from the other distractions of the body such as acidic pH, reticuloendothelial system, metabolic process. So, for better therapeutic outcome, it is important to incorporate herbal drugs or natural products in novel drug delivery systems [6].

## 2. HERBAL MEDICINE

Herbal medicine may be defined as a dosage form consisting of one or more plant parts or processed plant parts provide specific or other benefits in the diagnosis, treatment and prevention of diseases in human or animals and also may have nutritional value [7]. Herbal drugs constitute found in a major contribution to all the officially renowned systems such as Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. Herbal remedies are medicinal plants that contain as active ingredients plant materials such as juices, gums, fatty oils, essential oils and many other substances of these. They also include crude plant material such as leaves, fruit, seed, bark, root, stem, or

other parts of the plants entirely or fragmented by using different local methods of different countries like extraction, purification, fractionation etc [2].

## 3. DRUG DISCOVERY CHALLENGES FROM PLANTS AND RECENT ADVANCEMENT

Scientists will require improving the quality and quantity of the natural product compounds continuously that enter the drug development phase to keep pace with modern drug discovery process [8]. Discovery and development of plant-based drug products have traditionally been lengthier and more complex than other drug discovery methods [9]. Researchers of this arena also require collaboration with other academic departments such as biology, chemistry, ecology, and nutrition to continue their investigations on medicinal plants [10]. Nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS) are currently in wide use for modern drug discovery process, these methods could be applied to plant-based drug discovery to facilitate compound isolation [11]. In the medicinal plant-based lead discovery and optimization, high throughput X-ray crystallography could also be applied [12]. Another approach to improve herbal compound development may involve the establishment of the herbal compound and herbal compound derivatives library that combine the features of herbal compounds with combinatorial chemistry [13]. Though facing lots of challenges and difficulties by the scientists involved in drug discovery from medicinal plants, compounds isolated from medicinal plants can be predicted to remain an essential component in the search of a new chemical entity having therapeutic potential [14]. However, lots of research is going on in this field [15].

## 4. SCOPE OF NOVEL DRUG DELIVERY SYSTEM FOR HERBAL DRUGS

There is huge potential to utilize novel approaches of delivering herbal products, several researchers are working towards the development of novel drug delivery systems like mouth dissolving tablets, sustained and extended release formulations, muco-adhesive systems, transdermal dosage forms, microparticles, microcapsules, nanoparticles, implants etc. of herbs. Many of them have already reached to market and some of them are at the laboratory

stage [6]. Many drug molecules such as Digoxin, Quinine, Morphine, Atropine, Colchicine, Bromelain, etc had been isolated from the plants as their active components for the treatment of various diseases. Many of the plant-based herbal formulations have the potential to provide remedy of cancer and inflammation such as Curcumin, Triphala, Pomegranate, Kalonji, Sariva, etc [2]. Novel drug delivery systems have gained the popularity and importance to achieve modified delivery of herbal drugs, thereby increasing the therapeutic effect with lowering toxicity [16]. Lower bioavailability due to decrease drug absorption and lack of target specificity are the two major limitations of currently available formulations of herbal drugs [17].

Novel herbal drug delivery systems are designed to subdue the limitations of the currently available herbal drug formulations due to its wide range of advantage to mankind can be summarized as follows:

- The novel herbal drug delivery system can be used to achieve site specificity.
- Novel drug delivery system enhances the surface area of the drugs, therefore allows quicker absorption and rapid onset of action.
- The enhanced penetration of nanoparticles through Blood Brain Barrier (BBB) [5].

In recent past, much attention has been given to the development of novel herbal drug delivery system. Various kinds of novel herbal formulations such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microspheres, transferosomes, and ethosomes have been reported using bioactive plant extracts [18]. Many constituents of the herbal drugs will be degraded in the highly acidic pH of the stomach before reaching to the systemic circulation and other constituents may be subjected to first pass metabolism, resulting in reduced bioavailability of herbal drugs. If the drug does not reach in the optimum amount to the targeted area will fail to maintain “minimum effective level,” then there will be no therapeutic effect of the drug. Nanocarriers applying to herbal remedies will carry the optimum amount of the drug to their site of action bypassing all the barriers such as acidic pH of the stomach, liver metabolism and results in the prolonged action of the drug and rapid onset of action due to their small size [19]. Herbal products are considered as a potential candidate for delivery through the

novel delivery system because of the following properties:

- Many natural compounds were shown to produce better results without having side effects than many other drugs or surgical procedure.
- They can deliver mixtures of multi-functional molecules with potentiating and synergistic effects.
- They have a strong traditional or conceptual base and the potential to be useful as drugs in terms of safety and effectiveness whereas modern medicines have a very strong experimental basis for their use but are potentially toxic [20].

## 5. DIFFERENT CARRIERS FOR NOVEL DRUG DELIVERY SYSTEM OF HERBAL DRUGS

It is the method of drug delivery that has significant efficacy with minimum dosage and maximum benefits. As the drug delivery method can have an important effect on its efficacy, drug targeting is the potential way to direct the compound to the site of interest [21].

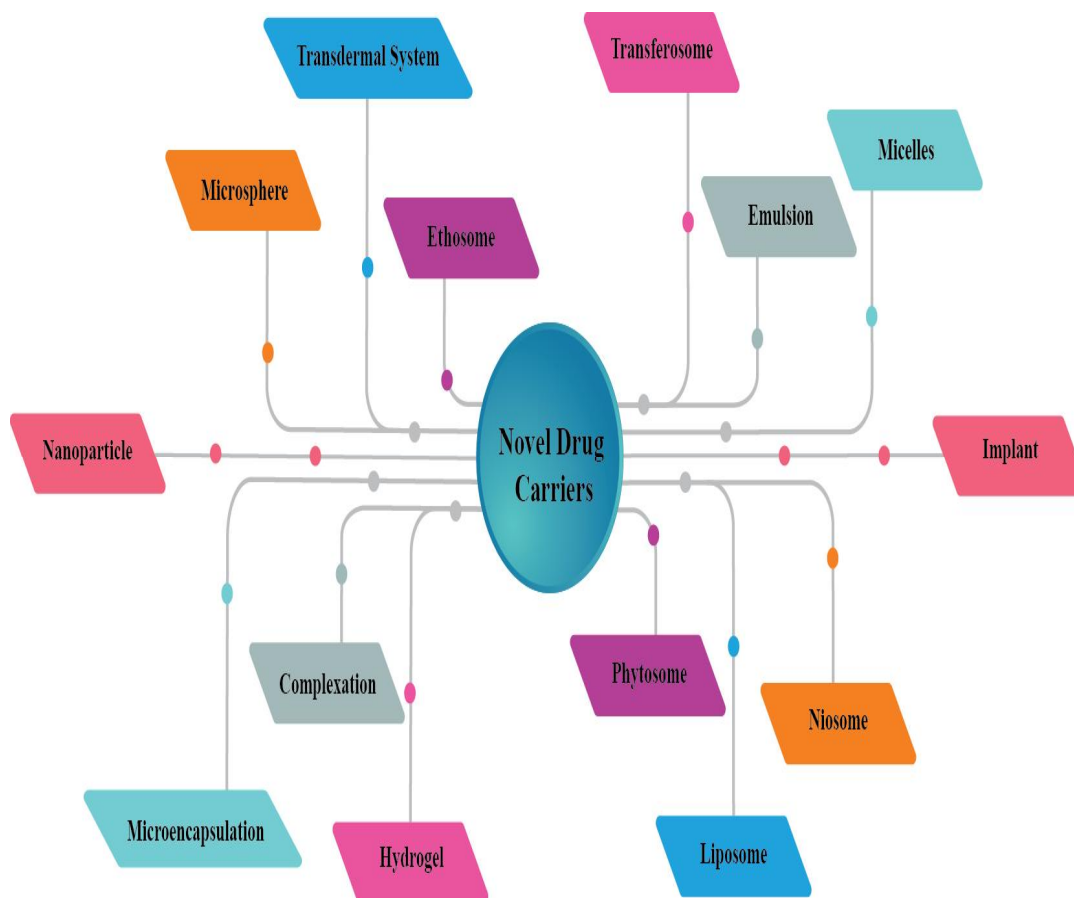
Different types of the carrier involved in a novel approach for administration of herbal drugs can be categorized as follows:

### 5.1 Phytosomes

The word ‘Phyto’ means plant and ‘some’ means cell-like [22]. Phytosomes are little cell-like structures. Phytosome is a novel form of formulations which contains the biologically active phytoconstituents of herb extract complexed with phospholipids that produce molecular complexes which is lipid compatible [23]. It is a newly developed and patented technology to incorporate water-soluble phytoconstituents or standardized plant extracts into phospholipids to generate lipid compatible molecular complexes. In certain literature, it is also referred as ribosome [24].

### Advantages of Phytosomes

- Phytosomes produces a cell-like structure where the valuable phytocomponents are protected from demolition by gut bacteria and digestive secretions.
- It shows better stability due to the formation of chemical bonds between phytoconstituents and phosphatidylcholine molecules.



**Fig. 1. Types of novel drug delivery systems**

- Phytosomes ensure target delivery of herbal drug to the respective tissues [25].
- It has a significantly greater therapeutic benefit because it increases the absorption of lipid insoluble polar phytoconstituents showing better bioavailability [26].
- Application in form of phytosome improves percutaneous absorption of phytoconstituents hence act as useful cosmetics [27].

systems can increase the therapeutic efficacy of herbal drugs. The liposomes encapsulate the solvents are spherical vesicles of 0.05-5.0  $\mu\text{m}$  diameter which are freely floating in the interior. Liposome enhances the ingredient solubility, bio-distribution, bioavailability, *in-vitro* and *in-vivo* stability and altered pharmacokinetics [29]. Herbal drug formulations available in the liposomal delivery system are summarized in Table 1.

## 5.2 Liposomes

Liposomes are microscopic vesicles composed of one or more concentric lipid bilayers, separated by an aqueous medium. Hydrophilic substances are encapsulated in the aqueous compartment, while adsorbed lipophiles are inserted into the membrane. Liposomes are classified according to their size, a number of lamellae, and surface charge. As to surface charge, liposomes are classified as anionic, cationic, or neutral [28]. Liposomal drug delivery

## Advantages of liposomes

- Liposome formulation increases the drug solubility and can produce controlled release and sustained formulation.
- The chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic phytoconstituent.
- The simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components [30].

### 5.3 Nanoparticles

Nanoparticles have a particle size in between 1-100 nm. Nanoparticles are composed of synthetic or semisynthetic polymers having nano or sub nano-sized structures. In nanotechnology, a small object that used as a whole unit with respect to its transport is defined as particle [31]. Nanoparticles can easily reach the effective site as the formulation is encapsulated in it easily. Microencapsulation of herbal extract in nanoparticulate is an effective way used to protect food ingredients or drug from volatile losses, deterioration, or interaction with other ingredients [29]. Nanoparticles show several advantages like solubility enhancement, efficacy enhancement, bioavailability enhancement, dose reduction and improved absorption of herbal medicines. Nanoparticles were developed with biocompatible and biodegradable polymers with uniform in size, spherical in shape and smooth surface to counter the poor solubility problem and toxicity of triptolide [32].

#### Advantages of herbal nanoparticle delivery system

- Nanoparticles have better efficacy as it enhances the herbal drug solubility and helps to deliver the drug to a specific site.
- Drug delivery in small particle size has quicker dissolution in the blood as it increases the total surface area of the drugs [33].

### 5.4 Microemulsions and Nanoemulsion

Microemulsions and nanoemulsions are O/W type emulsion having the size of several microns. They are used for the veterinary purpose for being nontoxic and nonirritant in nature [29]. The drug is packed in the inner phase and can release for a long time because of direct contact with the tissues. Lipophilic drugs as being made into o/w/o emulsion, macrophages phagocytosed the droplets of oil and increase its concentration in liver, kidney and spleen [34]. Some literature reported a herbal oil of *Petrodon emarginatus* as microemulsion showed improved anti-inflammatory activity [35].

### 5.5 Microsphere

In microspheres, drug is dispersed in the polymer within a matrix and released follow first order kinetics. It is a spherical shaped particle having

size ideally 1-300  $\mu\text{m}$ . At first, the dissolution media diffuse the matrix which makes the dispersed drug to solubilize in media and drug released. In another type microsphere, polymer show surface erosion behavior where the surface dissolved layer by layer and the release of drug occurs. Degradation and dissolution of the matrix control the release of drug from microsphere. The release of drug is affected by the type of matrix, size, and polymer concentration etc.

#### Advantages of microsphere formulations

- Administration of medication via microparticulate system is beneficial as they can be taken orally or injected and release profiles can be controlled and can even provide site targeted release [16].
- Zedoary oil and Quercetin microspheres therapeutic effectiveness are reported in the literature (Table 1).

### 5.6 Niosomes

Niosomes are formed usually by non-ionic surfactant of the alkyl or dialkyl polyglycerol and cholesterol. It is used as potential drug carriers similar to liposomes. Niosomes offer certain advantages over liposomes as being stable as it is able to encapsulate different types of drugs, economic and are different from liposomes [36]. Several niosome based formulation of herbal drugs are reported and summarized in the Table 1.

#### 5.6.1 Transdermal drug delivery system

Transdermal drug delivery system delivers the drug in a patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Transdermal drug delivery system (TDDS) recognized as a part of novel drug delivery systems as in recent time many of the drugs taken orally are found not to be as valuable as wanted [37]. An antismoking patch of nicotine for cessations of smoking and scopolamine patch for motion sickness are already employed in the market along with other herbal transdermal formulations [38].

#### Advantages of transdermal drug delivery

- The transdermal delivery system gives controlled drug delivery.
- Enhanced bioavailability [34].
- It is a beneficial alternative for unconscious and nauseated patients [37].

## 5.7 Ethosomes

Ethosomes are a sac-like system composed of a high concentration of ethanol and phospholipids. High concentration of ethanol in the sac enhances their permeability through the. Ethosomes delivered the drug in the form of a cream, gel for patient comfort [38].

### Advantages of Ethosome

- It increases the transdermal permeability of drug through the skin.
- It can entrap all types of drug molecules i.e. hydrophilic, lipophilic or amphiphilic [39].

Several autosomal formulations of herbal drugs are mentioned in Table 1.

## 5.8 Transferosomes

Transferosomes are sac-like vesicle composed of phospholipid that acts as potential carriers for the delivery of the drug through transdermal route. It overcomes the penetration difficulty through the stratum corneum. Due to their flexibility, It can easily penetrate through the intracellular pores of the skin. Colchicine delivery through transferosomes provides sustained, local and site-specific delivery and preventing it from the gastrointestinal side effects due to oral administration [40].

### Advantages of Transferosomes

- Transferosomes can deform and pass through narrow constriction without measurable loss.
- They have high entrapment efficiency, in case of the lipophilic drug near to 90%.
- Easy to scale up, as the procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives [41].

## 5.9 Polymeric Micelle Formulations

Micelles show readily controllable and specious pharmacological properties so they can be used to take a number of drugs. One of the unique and very useful properties of micelles is their capacity to solubilize solute molecules that are otherwise insoluble in aqueous solutions [28]. Micelles hold an inner hydrophobic core capable of solubilizing

lipophilic substances and an outer hydrophobic core which acts as the stabilizing interface between the internal hydrophobic core and external aqueous environment. Polymeric micelles composed of hydrophobic core reposed by the hydrophilic polymer chains revealed to the aqueous environment. Micelles are a very hopeful strategy to a broader range of different activity with a very higher selectivity [42]. Development of polymeric micelles of curcumin with increased solubility and excellent inhibitory effect on tumour cells because of their sustained drug release is reported in the literature [43].

## 5.10 Mucoadhesive Drug Delivery Systems

Bio adhesion is the concept where natural and synthetic materials adhere to biological surfaces. They are held together for prolonged period by interfacial forces. In pharmaceutical science, the attractive force between a biological material and mucus or mucous membrane is called muco adhesion. In addition, it was always a matter of great fascination that the development of oral muco adhesive system is a system which is efficient to adhere to particular gastrointestinal (GI) segments that would offer various advantages [44]. Muco adhesive formulations of Punica granatum flower extract (oral gel) for the treatment of recurrent aphthous stomatitis are evaluated for its effectiveness [45].

## 5.11 Complexation

The major problem in the formulation of the herbal dosage form is their poor solubility. To get the desired therapeutic concentration of the drug in systemic circulation an adequate solubility is a must. Complexation among molecules is the organization of molecules to form a non-bonded being with a well-defined stoichiometry. Various complexing agents such as EDTA polymers and cyclodextrins have been used for the complexation [46].

## 5.12 Hydrogels

The hydrogel is a network of cross-linked polymer gels that are three dimensional and hydrophilic. It can be made of any water-soluble polymer surrounded by a wide range of physical properties and chemical composition. Besides, they can be formulated in various ways of physical forms like micro particles, slabs, nanoparticles coatings, and films [47].

**Table 1. Formulations of herbal novel drug delivery system [33,36,38,47]**

<b>Formulation</b>	<b>Active ingredients</b>	<b>Application of herbal formulations</b>	<b>Indication</b>
Curcumin Phytosome	Curcumin	Increase antioxidant activity and increase bioavailability	Antioxidant, [33] Anticancer [47]
Green tea Phytosome	Pigallocatechin	Increase absorption	Nutraceutical, Systemic antioxidant, Anticancer [47]
Silymarin Liposome	Flavonol, Glycoside	Improved stability and permeation of silymarin	Hepatoprotective [47]
Catechins Liposome	Polyphenol	Improved in vivo deposition and loading of catechins	Antiviral, Ant oxidative, Anti-obesity, Anti-carcinogenic, Chemo preventive, Anti-inflammatory [33]
Berberine Nanoparticle	Berberine	H. pylori growth inhibition	Anti-neoplastic activity [33]
Ginseng Nanoparticle	Ginseng	Improvement in action and improvement in its stability	Antioxidant activity [47]
Azadirachtaindica Emulsion	Azadirachtaindica	The formulation has low toxicity	Acaricidal, Anti-fungal [47]
Marine Emulsion	Marine	Sustained-release formulation	Antibacterial, Anti-inflammatory [47]
Zedoary oil microspheres	Zedoary oil	Sustained release and Higher bioavailability	Hepatoprotective [36]
Quercetin microspheres	Quercetin	Significantly decreases the dose size	Anti cancer [47]
Colchicine Niosome	Colchicine	Prolonged release profile	Rheumatic complaints [36]
<i>Capsicum annum</i> Transfersome Formulation	Capsaicin	Increase skin penetration	Treatment of Rheumatism [47]
<i>Colchicum autumnale</i> Transfersome Formulation.	Colchicine	Reduction in GIT side effects	Treatment of Gout [47]
<i>Curcuma longa</i> Transfersome Formulation.	Curcumin	Increase skin permeability	Anti-inflammatory [38]
<i>Glycyrrhiza glabra</i> ethosome formulation	Ammonium glycyrrhizinate	Improved antiinflammatory activity and sustained release action	Treatment of Dermatitis, Eczema and Psoriasis [33]
<i>Cannabis sativa</i> ethosome formulation	Tetrahydrocannabinol-diol	Improved patient compliance and Increased skin permeation	Treatment of Rheumatoid Arthritis [47]
<i>Tripterygium Wilfordii</i> ethosome formulation	Triptolide	Increase in percutaneous permeability	Anti-inflammatory [38], Antitumour
Transdermal SCOP (Herbal Transdermal Patch)	Scopolamine	Improved patient compliance	Prevent Motion Sickness [38]
Antismoking Patch –Nicoderm CQ	Nicotine	Quit smoking	Antismoking Agent [38]

The promising potential of using hydrogels to combine medicinal herbs with synthetic drugs in one single treatment will act as an avenue for future research [48].

Some formulations of the herbal novel drug delivery system available in the market as summarized in the following table [38,47].

## 6. FUTURE PROSPECTIVE

The widespread uses of natural products with medicinal properties are obtained from commonly used herbs and medicinal plants [49]. Herbal medicines have been used vastly by the major part of the population for curing ailments. All over the world, the exploration has been going on herbal remedies. The development of herbal medicine in the drug delivery system in a number of organizations is being performed at basic and clinical trial levels. Though the herbal formulations are unexpected to cure diseases fully but they can assist in the better regulation of diseases by the patient himself. Besides, it can also improve the quality of life by giving nutritional supplement as well. The only necessity is to develop the better drug delivery system of such drugs at the sites and in the entire body in the doses which will not accommodate with the existing treatment. Toxicity & hypersensitivity reactions of some marked drugs may also overcome through the approach of different delivery of herbal drugs. Hence, using herbal medicine in the novel drug delivery system will increase its effectiveness for the treatment of many chronic diseases and health benefits. There are so many successful examples with evidence are present in the direction of nano research [50]. Herbal medicines are also improving resources of advantageous compounds including antioxidants and constituents that can be used in purposeful foods. This kind of collaborative research among the traditional herbal medicines and modern approaches of drug delivery system, i.e., "Nanotechnology" has established striking therapies to the pharmaceutical in near future that will improve the health of people. It is expected that the effectual and valuable topicality of natural and herbal products being applied with the nano carrier will enhance the significance future prospective [51].

## 7. CONCLUSION

Herbal drugs or plant actives contains a lot of therapeutic potentials that should be analyzed via application of novel drug delivery technology. This review gives information about novel drug delivery system in herbals, their types, formulation, uses of herbal drugs and current market status of novel drug delivery system of herbal medicines. This information is useful for the further research work, isolation of chemical entities from novel drug delivery system in herbals and formulation of novel drug delivery system in herbals. Herbal drugs have plenty of

therapeutic potentials which should be analyzed through some value added drug delivery systems. Molecular size and lipid solubility are the major factors for drug molecules to pass the biological membrane to be absorbed methodically following topical or oral administration. Many plant extracts despite having excellent *in vitro* bio-activity demonstrate less or no *in vivo* actions due to their improper molecular size or poor lipid solubility or both, resulting in poor bioavailability and absorption. Ascertained plant extracts or mainly polar phyto constituents like xanthenes, tannins, terpenoids, flavonoids when administered through novel drug delivery system show much better absorption profile which qualify them to cross the biological membrane, resulting in enhanced bioavailability. Hence more amount of active constituent happens present at the site of action like living, kidney, brain etc, at a similar dose as compared to the traditional plant extract or phytomolecule. Therefore, the therapeutic action becomes improved, more detectable and prolonged. Many of the excellent phyto constituents have been successfully released using the novel drug delivery system. Hence there is a high potential for the improvement of novel drug delivery systems for the plant actives and extracts. Herbal excipients are less expensive, freely available and non-toxic compared to their synthetic counterpart. Hence, in near future, there is going to be continued interest in the natural excipients to have better materials for drug delivery systems. Since ancient times, herbal medicines have been widely used all over the world and recognized by physicians, patients for their betterment. As they have higher therapeutic value and lower adverse effects compared to modern medicines. However, phyto therapeutics need a scientific approach to deliver the constituents in a novel manner to increase patient compliance and get off repeated administration. This can be accomplished by designing novel drug delivery systems for herbal constituents.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.



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