Novel Drug Delivery Systems for Phytoconstituents
Novel Drug Delivery Systems for Phytoconstituents

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Men and medicine are inseparable from time immemorial. The use of plants for therapeutic purposes by humans is an age-old practice. Herbal medicines are drugs that use plants, their parts, or products for prevention and treatment of diseases.

Herbal formulations are made from plants or their parts, whole extracts, or active concentrates, with or without excipients into safe, effective, and uniform composition medicinal products. The scientific method by which the plant bioactive concentrates are processed into safe medicinal products is called herbal formulation development. These phytoconstituents achieved from nature consist of full of wide biological therapeutic activities to treat various chronic diseases. However, various challenges exist to use them such as lesser aqueous solubility, poor permeation, and lack of targeting specificity.

Over the past two decades, significant advances have been made related to development of drug delivery systems for herbal products and extracts. Novel herbal drug delivery system opens new vistas for delivery of herbal drugs at the right place, at the right concentration, for the right period of time and also gives a scientific angle to verify the standardization of herbal drugs. The herbal drugs can be utilized in a better form with enhanced efficacy by incorporating them in modern dosage forms.

These modern approaches are termed novel drug delivery systems (NDDS), which contain polymeric nanocapsules, nanoparticles, nanoemulsions, liposomes, niosomes, phytosomes, microsphere, transferosomes, and ethosomes. All these novel systems are able to overcome the challenges associated with only herbal phytoconstituents. The drugs are delivered in a suitable formulation, keeping in view safety, efficacy, and acceptability among other factors, and the formulation is usually known as dosage form or drug delivery system.

Herbal drugs are becoming more popular in the modern world for their application to cure a variety of diseases with less toxic effects and better therapeutic effects. However, some limitations of herbal extracts/plant actives like instability in highly acidic pH, liver metabolism, etc. have led to drug levels below therapeutic concentration in the blood resulting in less or no therapeutic effect. Incorporation of novel drug delivery technology to herbal or plant actives minimizes the drug degradation or pre-systemic metabolism and serious side effects by accumulation of drugs to the non-targeted areas and improves the ease of administration in pediatric and geriatric patients.

For good bioavailability, natural products must have a good balance between hydrophilicity and lipophilicity. Many phytoconstituents like polyphenolics have good water solubility, but are, nevertheless, poorly absorbed either due to their multiple-ring large size molecules, which cannot be absorbed by simple diffusion, or due to their poor miscibility with oil and other lipids, severely limiting their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Thus, the nano-sized novel drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines.

A number of plant constituents like flavonoids, tannins, terpenoids, etc. show enhanced therapeutic effect at similar or less dose when incorporated into novel drug delivery vesicles as compared to conventional plant extracts. Hence, there is a great potential in development of novel drug delivery systems for valuable herbal drugs as it provides efficient and economical drug delivery.

In line with all these revolutionary progresses in the drug delivery field, *Novel Drug Delivery Systems for Phytoconstituents* is a compiled book analyzing the fundamental and more advanced aspects in the development of nanomedicines for herbal formulations. The selected book chapter contributions have been written by well-known experts in the field and comprise insights into the most promising moves toward superior drug-loaded nanoplatforms.

In this context, the first chapter is dedicated to current and future prospects of novel drug delivery systems, especially for phytoconstituents. These novel approaches of delivering herbal drugs would be able to enhance the efficacy and safety of phytoconstituents along with the increased stability of
the drug product. The second chapter is focused on various types of novel drug delivery systems for phytoconstituents, their advantages over conventional systems, and their potential applications in phytomedicine.

Chapters 3 through 5 discuss the delivery aspects, compositions, and applications with various strategies for liposomes and phytosomes including lipid-based nanoparticles: SLN, NLC, and MAD.

Chapters 6 and 7 focus on cosmeceutical applications of phytosomes as well as the role of major UV protecting agents from various plant sources and recent advancement in nano-medicine for improvement in context of UV protection, respectively. Chapter 8 exclusively emphasizes the development, optimization, characterization, and clinically therapeutic applications of ethosome formulations in treatment of melanoma and psoriasis. Chapter 9 focuses on the promising anticancer phytodrugs, including alkaloids, podophyllotoxin, combretastatins, and flavonoids, and the challenges in drug delivery. The promising micro/nano-carrier-based systems for better delivery of these anticancer phytodrugs were described.

Chapters 10 and 11 are exclusively dedicated to silymarin and discussing the role and application of diverse drug delivery systems studied so far. Liposomes, nanoparticles, micro-emulsions, and polymer-based systems are classified and the pros and cons of each system as well as benefits of nanoformulations for silymarin delivery that can be reconsidered with a much better and potentially beneficial role of phyto-antioxidant.

Chapter 12 extensively covers the innovative delivery systems for andrographolide delivery followed by a discussion on new delivery systems, their current producing methods, and their therapeutic role in improving the management of chronic illnesses. Chapter 13 is dedicated to the use of biocompatible natural and synthetic polymers able to formulate micro- and nanosystems with an improvement of the physicochemical, biological, and technological polyphenolic characteristics.

Chapters 14 and 15 focus on various delivery systems used for the controlled delivery of berberine and new delivery systems with enhanced affinity for the target while taking care of human safety and the environment respectively. Chapter 16 exclusively attracts the reader’s attention by describing the drug delivery for curcumin in special reference on novel delivery systems such as liposomes, nanoparticles, micelles, nanogels, nanoeмуulsions, nanocrystal suspensions, phytosome complexes, and inclusion complexes, which could open new avenues for enhancing the bioavailability and biological activity of curcumin.

This field of herbal drug delivery systems is dynamic and extensive. Probably it would need an encyclopedia to cover all the types of drug delivery systems. The aim of this book is to compile major drug delivery systems and offer a source of information for all those working in pharmaceutical academia as well as industry.

We also acknowledge our teachers Professor V.K. Dixit and Professor S.P Vyas for their valuable guidance. Special thanks to our families for their support and encouragement. We express our gratitude to the CRC Press publishing and Production team, specially Renu Upadhyay, Sikha Garg and Sundaramoorthy for their kind, proficient and encouraging guidance.

Last, but not least, we would like to express our sincere gratitude to all the authors who have taken time from their busy schedules to be part of this project and written wonderful chapters that added both the depth and value to this book. We welcome suggestions and criticisms for our readers.
Editors

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Section I

Drug Delivery Systems
1

Novel Drug Delivery Systems for Phytoconstituents: Current and Future Prospects

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1.1 Introduction

Since ancient times, herbal plants have been utilized to treat distinctive ailments because of their availability, accessibility, inherited practice, economic feasibility, and perceived efficacy. Ayurveda is the oldest health care system and describes a large number of medicinal plants with their curative properties.

In recent times, developed nations are turning to the utilization of traditional medicinal systems that include the use of herbal drugs and remedies, and as indicated by the World Health Organization (WHO), relatively 65% of the total population has incorporated plants as therapeutic agents into their main modality of health care. Furthermore, 25% of all drugs prescribed today originate from plants. Plant-determined constituents make up a huge portion of natural product based pharmaceuticals. Out of numerous families of secondary metabolites, alkaloids have contributed to the biggest number of medications like atropine (anticholinergics), opium alkaloids (analgesics), quinine (hostile to malarial), galantamine (anticholinesterases), vinblastine/vincristine (anticancer), steroids, etc. giving them an equally essential role to human well-being. They range from Na+/K+ pump-inhibiting cardiac glycosides from Digitalis spp., antineoplastic paclitaxel, antimalarial artemisinin, anti-inflammatory triptolide are also important for disease fighting (Mukhopadhyay et al., 2012).

Developed nations are swinging to the utilization of customary traditional medicinal systems in light of the fact that the phyto-constituents are potent in various remedial applications as they indicate defensive mechanism of action against various chronic diseases including diabetes, neurodegenerative illness, cancer, and cardiovascular disease. Yet at the same time there are a few challenges in appropriate use of phytochemicals because of their low water solubility, low absorptivity, and bioavailability. So a procedure of designed phytochemicals has been created to improve solubility, cell penetrability, proteolytic stability, and half-life of plant biomolecules (Upadhya, 2014).

The research and development push is focused on development of new creative and innovative delivery systems for plant based drugs. Phytoconstituents obtained from plants generally possess an inherent drawback of limited oral bio availability and instability owing to their hydrophilic nature. These water solvent phytoconstituents (e.g., tannins, flavonoids) have a poor lipophilicity and large atomic size, which
prevents their entrance through the cell membrane (Kadu and Apte, 2011). To tackle this issue Indena created Phytosome innovation, which essentially conjugates a hydrophilic phytoconstituent to a phospholipid through hydrogen bonds. In Phytosome, phospholipid and phytoconstituent are available in a specific stoichiometric proportion of 2:1 or 1:2 (Bhattacharya, 2009).

Recently, there has been growing enthusiasm about the advancement of novel drug delivery systems for phytoconstituent. The novel carriers should ideally fulfill two essentials. Firstly, it ought to deliver the drug at a rate directed by the requirements of the body, over the period of treatment. Furthermore, it should channel the active substance of the herbal drug to the site of action. Conventional dosage forms including delayed release dosage forms can’t meet these requirements. In phyto-formulation research, developing dosage forms (strong lipid nanoparticles, polymeric nanoparticles and nanocapsules, liposomes, nanoemulsion, phytosomes, etc.) have various advantages for herbal drugs, including improvement of solubility and bioavailability, improvement of pharmacological action, protection from toxicity, improvement of stability, enhancing tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation, and so on. Accordingly, the nano sized novel drug delivery systems of herbal drugs have a potential future for upgrading the action and defeating issues related with plant constituents (Ajazuddin and Saraf, 2010) (Figure 1.1).

1.2 Requirements for Novel Drug Delivery Systems for Phytoconstituents

Because of the complex nature of herbal extracts/constituents, high doses, poor bioavailability, and dose recurrence, their use in the modern medicinal system is limited. The three principle objectives of novel drug delivery systems (NDDS) is by giving sustained drug release, selected targeting to the site of action, and expanded patient compliance. NDDS lessen the frequency of dose as well as diminish peak and valley variances, which lead to improved bioavailability. The uses of NDDS in phytopharmaceuticals have been generally explored, and different marketed formulations of phytoconstituents are accessible in the worldwide market which individuals will consume and find beneficial (Singh, 2015). The proposed section will be useful in growing new delivery systems, which will overcome these issues related with traditional herbal extracts. This will investigate the capability and potential of herbal extracts with blending of modern industrial dimension, and ultimately outcomes in appropriate usage of herbal wealth of the state with helpful in enhancing socio-economic condition of the state.

The necessities of novel drug delivery systems of herbal medication over conventional herbal extracts include the following (Sharma, 2014):

- To increase the bio-availability of herbal extracts. They appear ready to convey high concentrations of medications to disease sites as a result of their unique size and high loading capacities.
- To deliver the medication in small particle sizes that improve the whole surface area of the drugs dispensing quicker dissolution in the blood.
- The effort appears to persist at the sites for the more extended periods. It shows an EPR (improved pervasion and maintenance) effect, i.e., improved permeation through the barriers due to the small size and retention because of poor lymphatic drainage such in as tumors.
- To assure localized delivery, i.e., to the liver and so on, by novel carrier systems. It exhibits passive targeting to the disease site of action without the addition of a specific ligand moiety.
- To reduce side effects.
- To make uniform dosage form and reduce doses of the drug formulation.
- To keep the degradation of herbal extract in the GIT.
- Effective chloroform, petroleum ether, acetone, and methanolic extracts are accessible, which may not be appropriate for delivery as such.
1.3 Current Developments in the Delivery System of Herbals

Novel drug delivery system (Table 1.1) is a novel way to deal with medication that is held to the constraints of conventional drug delivery systems. India has a vast knowledge base of Ayurveda whose potential is just being recognized in recent years. In any case, the formulation utilized for administering herbal drugs to the patient is conventional and outdated, bringing about decreased capability of the drug. In the event that the novel drug delivery technology is coupled in herbal drugs, it might help in expanding adequacy and decrease the side effects of different herbal compounds and herbs. This is the essential thought behind incorporating novel techniques for drug delivery in herbal medicines. Along these lines it is critical to incorporate novel drug delivery systems and Indian Ayurvedic medicines to fight progressively serious illnesses. For quite a while herbal medicines were not considered for improvement as novel formulations due to
Novel Drug Delivery Systems for Phytoconstituents

The absence of scientific justification and processing difficulty, for example, standardization, extraction, isolation, and identification of individual constituents in complex polyherbal systems. Notwithstanding, present day phytopharmaceutical research can resolve the scientific requirements (for example, determination of pharmacokinetics, accurate dose required, mechanism of action, site of action, etc.) of herbal medicines to be incorporated in novel drug delivery, for example, liposomes, solid lipid nanoparticles, microsphere, ethosomes, transferosomes, microbubbles, carbon nanotubes, hydrogel, nanoparticles, microemulsions, matrix systems, solid dispersions, and copolymer micelles (Devi et al., 2010).

### 1.4 Limitations of Novel Delivery Systems of Herbals

Limitations of NDDS include poor storage stability, poor encapsulation efficiency, lengthy production procedures, and when chemical cross-linking is involved, possible inactivation of herbal components. Better understanding of metabolic pathways is important to ensure the safety of nanocarriers in clinical applications (Liu and Feng, 2015). Complexity of conducting clinical research in phytoconstituents...
toxicity as well as safety evaluation in animals are observed (Devi et al., 2010). Clinical assessments required for the herb–drug interaction potential of phytoconstituents incorporating these novel formulations. Regulatory requirement required for phytoconstituents extract interaction with other medicine (Gurley, 2011). Future study required on explanation of metabolic pathways (yielding potentially new active compounds), and the evaluation of elimination routes and their kinetics (Bhattaram et al., 2002).

1.5 Conclusion

The modern prospect of plant constituent delivery development is extremely encouraging. There is incredible capability of herbal delivery to be a safe, effective, convenient, and economic treatment. In any case, herbal formulation development studies are usually exploratory to date and need active expansion. It is widely expected that utilization of herbal drug delivery will make novel therapeutics, changing the prospect of phyto-pharmaceutical industries. Development of phyto-constituent delivery can help in achieving consistent quality, bioavailability, and therapeutic effects of herbal drugs and products. Different phyto-constituent delivery systems are being researched, either in development or in clinical stages, and there are numerous areas of interest where there will be effective and safer targeted therapeutics for a numerous of clinical applications. With the improvement in materials and equipment, an ever increasing number of herbal drugs will undoubtedly be formulated in the future. Effectiveness, stability studies, and shelf life of herbal drugs can be extensively improved by formulation development. It will be evolving very soon for the benefit of humanity at large.
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