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Review article

Recent expansion of pharmaceutical nanotechnologies and targeting strategies in the field of phytopharmaceuticals for the delivery of herbal extracts and bioactives

Amit Alexander [a], Ajazuddin [a], Ravish J. Patel [b], Swarnlata Saraf [c], Shailendra Saraf [c,*]

[a] Rungta College of Pharmaceutical Sciences and Research, Kohka-Kurud Road, Bhilai, Chhattisgarh 490024, India
[b] Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, Anand, Gujarat, India
[c] University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh 492010, India

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ABSTRACT

Application of pharmaceutical nanotechnology (nanomedicines) for plant actives and extracts, is gaining a tremendous growth and interest among the scientists. This emerging herbal revolution has headed towards the development of another approaches for the delivery of poorly soluble herbal bioactives and plant extracts for enhancing their bioavailability and efficacy. In the same context, a majority of pharmaceutical nanotechnologies and targeting strategies including phytosomes, nanoparticles, hydrogels, microspheres, transferosomes and ethosomes, self nano emulsifying drug delivery systems (SNEDDS), self micro emulsifying drug delivery systems (SMEDDS) has been applied for the delivery of bioactives and plant extracts and were identified and explored. These pharmaceutical nanotechnologies have been proven to be the most efficient and reliable delivery systems, as these enhance the solubility, absorption, pharmacokinetics, bioavailability and provide protection from toxicity. Considering these aspects, the present review highlights the present scenario related to the expansion of novel herbal formulations utilizing the nanotechnologies and compilation of their delivery types and mechanism, methodology, loaded drug, drug size, entrapment efficiency of drug, *in vivo* activity and its application. Moreover, this review article provides an understanding of therapeutic efficacy of the herbal medicines to be loaded into the novel drug delivery system for various biomedical applications.

Contents

* Corresponding author at: Director, University Institute of Pharmacy, Dean, Faculty of Technology, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, 492010, India.
E-mail addresses: itsmeamitalex@gmail.com (A. Alexander), write2ajaz@gmail.com (Ajazuddin), ravishpatel.ph@charusat.ac.in (R.J. Patel), swarnlata_saraf@rediffmail.com (S. Saraf), professorshailendrasaraf@gmail.com, shailendrasaraf@rediffmail.com (S. Saraf).

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1. Introduction

Pharmaceutical nanotechnology (nanomedicines), remains to be the most suitable approach to deliver a bioactive or drug, in to the body. Nanomedicines must have the capability to deliver the drug to achieve effective concentration within the therapeutic window over a desired period. In addition, nanomedicines must be efficient enough to deliver a drug to the targeted site. In the past few years, many innovators and scientist have utilized the nanomedicines for the delivery of plant bioactives or herbal extracts. One of the biggest challenges for the use of herbal bioactives is their poor solubility and bioavailability. These limitations could be resolved by reducing the size of the bioactive to enhance the solubility and increasing the bioavailability thereof [1–3]. Thus, it is important to expand the boundaries of phytopharmaceuticals as far as its therapeutic efficacy of herbal bioactive is concerned. A number of nanodosage forms can be developed like, liposomes, solid lipid nanoparticles, nanoemulsion, nanocapsules and phytosomes®. Among these, liposome has the capability to encapsulate both hydrophilic and hydrophobic drugs, including its unique inherent property of being biodegradable and biocompatible. One of the most prominent methods to deliver an anticancer drug is increasing its concentration in the tumor cell by the use of liposomal formulations. Another approach is the application of enhanced permeability and retention (EPR) effect phenomenon to lower the exposure in tissues [4–10]. There are many properties of liposomes, that makes it more preferable delivery system for these herbal bioactives, like its biocompatibility, drug loading efficiency for hydrophilic, lipophilic and amphiphilic compounds. Liposomes by changing the bilayer chemical composition can regulate the pharmacokinetic properties of a drug [8,11–14]. Reticuloendothelial system (RES), entrapped most of the conventional liposomes loaded with various herbal bioactives [2,15,16]. In addition, these nano vesicular systems including nanoemulsion, ethosomes and transferosomes for loading of herbal bioactives and are discussed ahead [17]. Exploiting the use of phospholipids complexation, like herbosomes or phytosomes® of these herbal bioactives in recent years emerged as an important approach the enhancement of bioavailability of a numerous insoluble plant constituents. Incorporation of phospholipid molecules comprising phosphatidylcholine forms a complex with standardized herbal extracts and improves its permeation across the membrane. This in turn also increases the systemic bioavailability of drug by improving the water-oil partition coefficient. Water-soluble drugs when loaded to these phospholipid complexes significantly improves the bioavailability of drugs due to enhanced penetration *via* the lipoidal plasma membrane. In contrast, water insoluble drugs when loaded to the same; improve the bioavailability of drug because of its enhanced solubility in gastric environment [18–21]. However, we have previously reported some earlier works related to this area [22]. Apart from that, in the present article, we have coveredsome remarkable findings of the past couple of years, highlighting the importance of pharmaceutical nanotechnology in the efficient delivery and improved pharmacokinetics of herbal bioactives like *Berberine*, *Fisetin*, *Jaboticaba and Chelerythrine etc.*

2. Green technologies for standardization

The green technology aims to prevent the natural environment by minimizing the application of hazardous substances. The principle behind the green chemistry is to facilitate the environment friendly extraction techniques and to eliminate the use of harsh organic solvents for the same. Conventional extraction techniques requires large amount of samples, organic solvents, sorbents and time. The organic solvents used are not environmentally friendly and expensive too. To execute these technologies it is very important for one to understand the in depth of all the emerging technologies like, Ultrasound-assisted Extraction (UAE), Supercritical-fluid extraction (SFE), Microwave-assisted extraction (MAE) and Pressurized-liquid extraction (PLE)/Accelerated-solvent extraction (ASE). In case of UAE, only a very small volume (1–15 ml) of organic solvent and an ultrasonic probe is required to isolate the compound from the plant. Currently, UAE application for the extraction is very limited as the energy consumption for the pretreatment does not improved significantly. Compared to various other extraction processes UAE showed better extraction results for example *Salvia* species [23]. Likewise, fluids like carbon dioxide remain liquid and gas at a point above critical temperature (31.1 °C) and pressure (74 bar) are designated as supercritical fluids. These are the most efficient extraction technology, as CO_2 is non-flammable, inexpensive, and abundantly available and environment friendly. SFE ensures that the final product must be free from organic solvents and degradation free too. The only limitation of SFE is its high cost for the maintenance of the high pressure. Essential oils, carotenoids, tocopherols and phenolic compounds were extensively extracted by the use of SFE [24–27]. Studies show that the extraction yield of *Cyperus rotundud* Linn was remarkably higher than soxhlation with *n*-hexane [27]. Similarly, MAE is also widely used for the extraction process as it uses ILs (ionic liquids) as having versatile solvent properties. ILs is more thermal stable, tunable viscosity, miscible in organic and water, wide liquid range, no vapor pressure and possesses excellent solubility [28]. On the other hand, non-ionizing electromagnetic waves (microwaves) comprise a magnetic field and an electric field perpendicularly oscillating to each other in a frequency range of 0.3 to 300 GHz. Amazingly, microwaves can penetrate into the substance to generate the heat among the polar component for extraction by dipole rotation and ionic conduction [29]. MAE efficiency could be reduced by various factors like, moisture content, microwave radiation duration, temperature, pressure and number of extraction cycle. MAE can be used for various thermo labile compounds like *Gastrodia elatea*, rebaudiside A from *Stevia rebaudiana* and stevioside [30,31]. Moreover, PLE/ASE commonly referred to pressurized solvent extraction and is aligned to the principle of pressurized hot-water extraction (PHWE), subcritical water extraction (SWE) and when water is used for extraction is known as superheated water extraction. Extraction took place using elevated pressure and temperature. In PLE, the elevated pressure increases the solvent's boiling point facilitating extraction at temperature beyond the boiling point of the solvent [32]. Water content influence the extraction process by PLE. Using an inert sorbent (*e.g.* diatomaceous earth, sodium sulfate, *etc.*) along with the plant sample is put together tightly to stainless steel cell under closed flow-through system. Two optional set up includes static and dynamic processes. This involves continuous pumping of solvent takes place and in contrast a constant flow rate is maintained during the static mode. While in static mode, the extraction time is predetermined once the required temperature and pressure achieved (5–15 min/cycle). Extraction of thermo labile compounds like gastrodin and vanillyl alcohol in *Gastrodia elata* Blume is few example of the successful extraction by the use of PLE.

3. Development and application of polymeric systems (micro-, nano-) containing herbal

Nanotechnology intended to produce formulations in Nano size range. Now a day, nanotechnology has arose as a multipurpose drug delivery system based on the dispersion level of nano objects. These nano-ranged delivery systems can immediately release the drug in a free form under dilution in the biological fluids. Few other types of applications are the compatibility of nano-size with the design of the drug delivery at the cellular and sub-cellular levels. In lieu of loading of synthetic drug in nano carrier, herbal compounds have gain an outstanding recognition and acceptance as far as nanotechnologies are concerned. Here we have underlined the silent features of these drug delivery systems like, Phytosomes® (phyto-phospholipid complex), Liposomes, PEGylated liposomes, Niosomes, Nanoparticles, Microspheres, Emulsions and hydrogels.