Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Novel Drug Delivery Formulations of Herbal Bioactive Molecules

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ARTICLE DETAILS

Article history:
Received on 9 February 2021
Modified on 6 March 2021
Accepted on 13 March 2021

Keywords:
Herbal Bioactive Molecules,
Drug Delivery,
Bioavailability,
Formulations,
Vesicular Drug Delivery System.

ABSTRACT

The various novel drug delivery approaches for the therapeutic molecule are widely seeking attention in the field of biomedical science. However, the accuracy and efficacy of the drug is a major issue of concern. However, the herbal drug therapy has been in use from thousands of the years or from the ancient time to treat the patients. Hence the use of pure active chemical of the herbal isolate can be an alternative approach which may resolve the issue. We utilized multiple databases, PubMed (Medline), EMBASE and Google Scholar for literature search. The scientists and researchers are trying to apply the current advanced drug delivery concept on the herbal medicines to reduce the unwanted pharmacological and physiochemical side effects of the therapeutic molecules. There are various novel drug delivery systems which are being used for the delivery of the herbal bioactive molecules, such as the polymeric micelle, injectable hydrogel, Nano gel, microsphere, polymeric nanoparticles, Nanoemulsions, liposomes, Nanocapsules, phytosomes, dendrimer, transferosomes, and ethosomes. These formulations have a great number of advantages like the enhancement of drug solubility, bioavailability, dose reduction, drug distribution, drug stability, sustained delivery, protection from the drug degradation and minimization of the adverse effects and toxicity. The present review highlights the existing research and development for the herbal bioactive molecules and summarizes their preparation methodologies, characterization techniques, route of administration, and type of active ingredients, size distribution, pharmacological activity and applications of novel herbal formulations.

INTRODUCTION

Nowadays, in the field of pharmacology, finding or development of new pharmaceutical active ingredients are as important as to develop suitable drug delivery system. Research is focused on pharmacological action, dose, side effects, route of administration, pharmacokinetic and pharmacodynamics correlation to understand the overall mechanism which makes the drug molecule safer, effective and also ensures patient's compliance [1-3]. In this area, the first major task is to isolate the pure bioactive herbal molecules from crude product, followed by evaluation of quality, purity testing, pharmacokinetics, and pharmacodynamics [4, 5]. Every single new molecule needs validation for isolation, characterization and activity evaluation [6].

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India has an immense knowledge base of Ayurveda, whose potential is only being realized in the recent years. The medicines are available in the Ayurveda to treat the-various disease conditions of individuals [4], but the major issue is partial failure to understand the exact mechanism of action and about the required dose of active ingredients [7]. Hence, we cannot achieve the 100 % accuracy and efficacy of the drugs. Along with that the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug [8]. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. The novel drug delivery system has some essential features such as the prolonged drug delivery rate and accurate site of action [4, 6, 9]. Previously there were many difficulties to develop a novel herbal medicine as lack of scientific validation and processing

techniques, such as, extraction, standardization and identification of individual drug components in complex poly herbal systems [10]. Interestingly the modern phytopharmaceutical research have solved the many scientific necessities to develop a herbal medicine (for example pharmacokinetics of drug, mechanism of action, site of action, accurate dose required etc.) and makes herbal medicines to be incorporated in novel drug delivery system, such as liposomes, solid lipid nanoparticles, microemulsions, nanoparticles, phytosomes, matrix systems, solid dispersions, and so on [10, 11]. In the current scenario peoples are inclining to herbal medicines, it may because of, concern over the dependence and safety of drugs and surgery, inefficiency of medicines to treat many of the most common health conditions and many natural measures are being shown to produce better results than drugs or surgery with no side effects [8, 12]. It is also evident that the current drug treatments just suppress symptoms and overlook the underlying disease processes. However, many herbal products seem to address the cause of many diseases and produce superior clinical results [13].

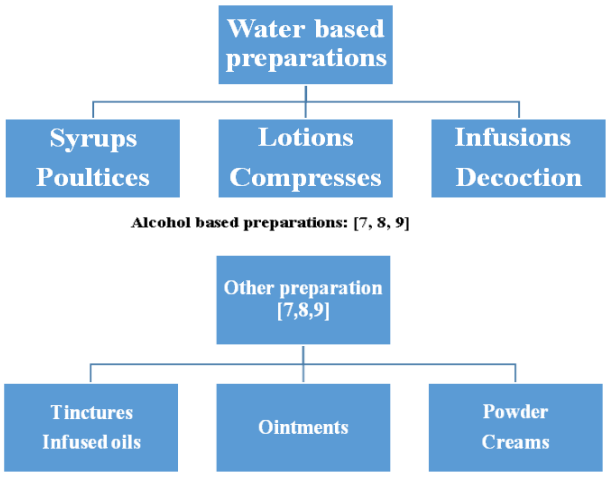
Method

We utilized multiple databases, PubMed (Medline), EMBASE and Google Scholar for literature search.

Discussion

Herbal Medicine

The herbal drugs are mainly single or mixture of secondary metabolites such as alkaloids, glycosides, terpenoids, oleo-gum-resin, phenolic etc., and primarily produced by plants for the self-defence purpose [7, 14]. But the major issue is that all secondary metabolites are not water soluble. Some of them are highly lipophilic and some of them are water soluble.



A good water-soluble secondary metabolite has a medicinal implication. The water solubility can be enhanced by the preparation of various salt forms. However, the salt formation is not possible for all the chemicals. In this case, various advanced techniques are required to deliver drugs [15, 16].

Terpenoids

The isoprenoids or terpenes are one of the most distinct categories of metabolites. Terpenoids are the most diverse and widest family of natural products. These vary in the sizes and structures. The structures of terpenes vary from linear molecules to polycyclic molecules and their size ranges from the five-carbon (C_5) hemiterpenes to natural rubber, containing thousands of isoprene monomer blocks. All terpenoids are synthesized by the condensation of isoprene blocks (C_5) and are sorted by the number of five-carbon units available in the core structure. Several flavoring and aromatic molecules, like as Menthol, Geraniol, Linalool, and caryophyllene are developed by monoterpenes (C_{10}), with two isoprene monomer blocks, and sesquiterpenes (C_{15}), with three isoprene monomer blocks. Some other bioactive molecules, e.g. diterpenes (C_{20}), triterpenes (C_{30}) and tetraterpenes (C_{40}) exhibit unique features [17, 18].

Phenolics

Phenolic is a major secondary metabolic product in the plant kingdom. It has single aromatic ring compound to large complex tannins and derived polyphenols. It has either flavonoids or non-flavonoids [19].

Alkaloids

Alkaloids belong to the family of naturally occurring chemical compounds, having predominant basic nitrogen atoms, and has several relevant molecules which possess weakly acidic or neutral characteristics. The various synthetically prepared molecules possess the same structure are also named as alkaloids. Hydrogen, nitrogen, and carbon are the main constituents in alkaloids while sulfur and oxygen also present in alkaloids. Bromine, phosphorus, and chlorine are rarely found in the alkaloids [20, 21].

Alkaloids are synthesized by plants, bacteria, animals and fungi. Crude alkaloids are extracted from the source, followed by purification and separation by acid-base extraction. Alkaloids are common in some specific groups of flowering plant species. More than three thousand types of

different alkaloids have been recognized among 4,000 plant varieties. There are alkaloid-containing families like Opium poppy, ergot fungus Ranunculaceae, Amaryllidaceae and Solanaceae. Some animal species also contain alkaloids, for example, Castor Canadensis and poison-dart frogs [20-22].

Alkaloids confirm broad spectrum of pharmacological activities, such as anti-asthma (Ephedrine), antimalarial (Quinine), anticancer (Homoharringtonine), vasodilatory (vincamine), cholinomimetic (Galantamine), antiarrhythmic (Quinidine), antibacterial (Chelerythrine), analgesic (Morphine), and antihyperglycemic activities (Piperine), for which they are in therapeutic use since ancient times.

Some of the alkaloids exhibit psychotropic effect (psilocin) and stimulant effect (cocaine, nicotine, caffeine, and theobromine). These are employed in recreational drugs or as an entheogenic ritual. Many alkaloids are toxic (atropine and tubocurarine).The herbal secondary metabolites and their applications are described in Fig. 1 [20, 23, 24].

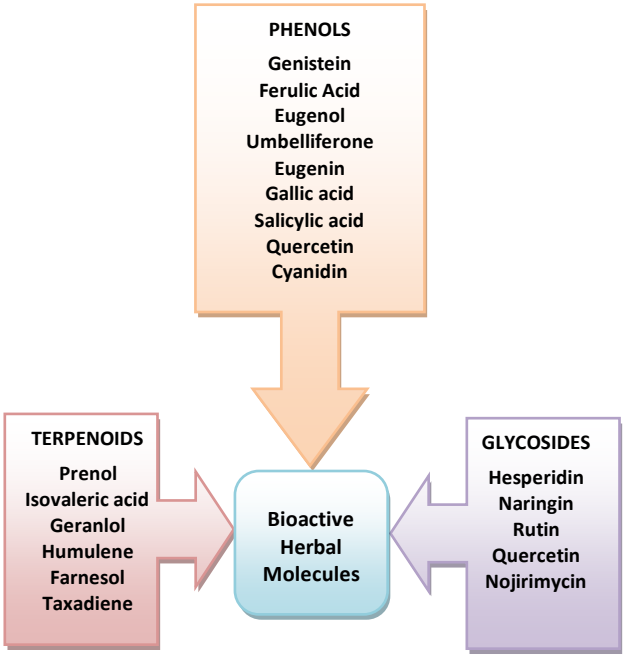


Figure 1: List of plant secondary metabolites and pharmacological classification of herbal drugs.

Advanced Drug Delivery System and Formulations

There are many advantages for the usage of Nano dosage forms of the herbal active bio molecules. The nano dosage forms like nanoemulsion, polymeric micelles, liposomes, spherosomes, solid lipid nanoparticles, and metal nanoparticles conjugate with the active biomolecules.

The advanced drug delivery formulations enhance the bioactive molecule solubility, stability, bioavailability, tissue macrophage distribution, and localization, clearance from the body, metabolism, prolonged release and minimize the toxic side effects, bio magnification, plasma protein binding, degradation of the bioactive herbal molecules. Hence the nano-sized formulations of bioactive herbal molecules improve their pharmacological activity and overwhelming hitches related to crude herbal medicines. Liposomes, micelles, nanoparticles are biocompatible/biodegradable carriers. These are able to encapsulate both type of molecules, hydrophilic as well as hydrophobic ingredients [15, 25].

The amphiphilic polymeric nanoparticles like micelles, liposomes improve the therapeutic index of several drugs. This is required to enhance the bioavailability and tissue permeability of the active ingredient. It increases the drug concentration above the minimum inhibitory concentration, prolong and control release over the time, trigger release as well as minimize the side effects and dose frequency e.g; anti-cancer drugs. These formulations offer the site targeted drug delivery by tagging the molecular markers over the surface of the liposome, polymeric micelles, and nanoparticles such as folate, biotin, streptavidin, glucosamine, and ester and thiol linkage in the polymers. All promote the site-directed delivery which overcomes the problem of the non-targeted systemic toxicity of the drugs. Nano-sized drug delivery formulation having several others advantages [25, 26] like;

1) Easy and tunable body clearance, which can be customized according to the requirement.
2) Biocompatible and biodegradable FDA approved polymeric materials.
3) Avoids the non-targeted drug delivery and minimize the toxicity of cytotoxic drugs such as anti-cancer agents.
4) Regulate the release of the herbal bioactive therapeutics molecules.
5) Easy alteration in the pharmacokinetic properties of herbal bioactive therapeutics by varying the chemical structure of the polymers.
6) Nano size formulations (< 70 nm) could easily pass through the reticuloendothelial system.

Likewise, the other polymeric nanocarriers systems such as dendrimers, ethosomes nano-emulsion, metal nanoparticles conjugate, and transferosomes, neosomes, are extremely useful associations and find numerous benefits in the delivery of the herbal bioactive compound delivery

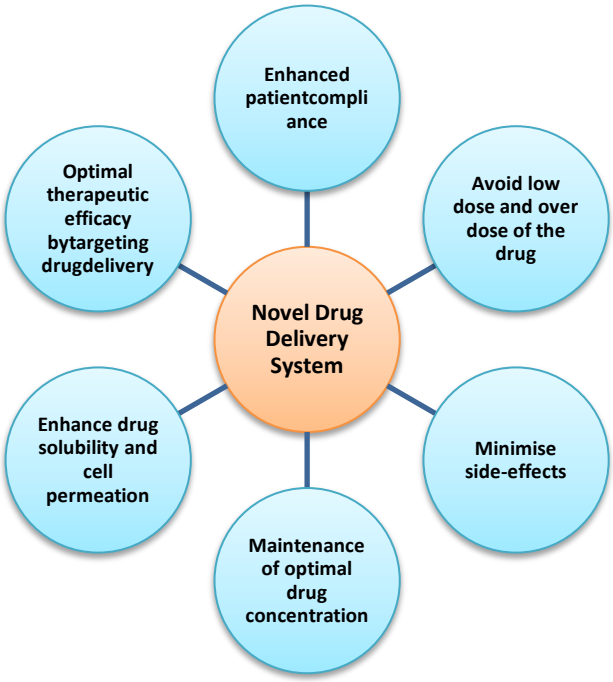


Figure 2: Advantages of novel drug delivery system

Advanced Vesicular Drug Delivery System

The lipid-based vesicular drug delivery system has well order dissociation. The vesicular drug delivery systems have capability to localize the delivery of drug at the site of treatment or organ of action; therefore these are mainly important for the targeted delivery of drugs or herbal bioactive molecules. By this, the concentration of herbal bioactive molecules could be minimised at the other non- targeted sites in the body.

Several types of formulations are available [27-30], such as Liposomes, Emulsomes, Transferosomes, Pharmacosomes, Virosomes, Enzymosomes, Ethosomes, Sphingosomes, Site specific targeting with Non- lipoidal biocarriers Aquasomes, Bilosomes and Niosomes.

The advantages of the vesicular system are as follows.

1. Enhance bioavailability of drugs
2. Avoid the fast drug metabolism by physiological factors.
3. Prolong the circulation life time of drugs
4. Site directed delivery of drug molecules by tagging with molecular markers.
5. Solve the drug stability and solubility problems.
6. The toxicity of certain molecules could be overcome through this approach.

Phytosomes

Phytosome is a combination of herbal bioactive molecules with suitable phospholipid part that are frequently lecithin. Phytosome enhance the absorption of crude herbal extracts or isolated bioactive molecules. The potency of any herbal bioactive molecule is mainly dependent on their delivery route, site, quantity and minimum effective concentration for pharmacological action. Phytosome is newly introduced into the herbal bioactive molecules formulations; that facilitates the better absorption and better bioavailability. Currently many predominant diseases and disorders are being treated by herbal bioactive molecules. Numerous herbal, phytoconstituents and extracts showed outstanding bioactivity *in vitro* experiments but they did not show at all *in-vivo* activity due to their limited lipid solubility or inappropriate molecular size or both, resulting into poor systemic absorption and bioavailability. Comparative studies have shown improved results for phytosome based drug delivery system over the conventional phosphatidylcholine based formulation of herbal active constituents. The herbal bioactive molecule via the outer membrane of gastrointestinal epithelial cells consequently gains the access to the circulation, which has better pharmacological and pharmacokinetic parameter, leading to its application in the treatment of the chronic and acute hepatic diseases [27, 31].

Nanoemulsion

Nanoemulsion is a type of emulsion that can load and release the herbal bioactive molecules in controlled manner. The size is ranges from 70-100 nm. It appears transparent due to its small size and Brownian motion. It prevents sedimentation or creaming. Hence it offers improve life span. Microemulsions are metastable. It can be diluted with water or buffer without changing the droplet size distribution. Nanonoemulsion are thermodynamically stable system, where two immiscible liquid (hydrophilic and hydrophobic) mix to form a single phase with the usage of small amount of appropriate surfactant. Nanoemulsion can be

prepared by high speed and pressure homoginization. The size of Nanoemulsion is small up to 1 nm. The size can be further decreased by micro fluidization techniques with use of micro fluidizer [30, 32, 33]. The following parameters need to be evaluated for microemulsion;

1. U.V. Spectrophotometer: Loading and release capacity of micro emulsion of herbal bioactive molecule can be evaluated through the UV and the transparency of microemulsion formulation could also be determined by measuring percentage light transmittance.
2. Dynamic Light Scattering (DLS): The droplet size and distribution analysis.
3. Zeta-Potential: Charge base stability and interaction analysis
4. Viscosity
5. Transmission Electron Microscopy (TEM): surface morphology and size analysis can be performing through TEM.

Emulsions

Emulsions are thermodynamically unstable, biphasic liquid dosage form. It has at least two immiscible liquids, one of which is dispersed as globule in another liquid, stabilized by emulsifying agent. The average droplet size of the globule is less than 0.2 μm [27, 32].

Phases of Emulsion

1. **Dispersed phase:** This is suspended in continuous phase as droplets.
2. **Continuous phase:** This contains droplets of dispersed phase.
3. **Emulsifier:** This is a substance which stabilize the emulsion

Types of Emulsion

1. Simple/Macro emulsion
2. Oil in water (o/w)
3. Water in oil (w/o)
4. Multiple emulsion
5. Oil in water in oil
6. Water in oil in water
7. Micro emulsion: Clear transparent solution

Particle size ranges from 10-200nm.

Suspension

Suspensions are thermodynamically unstable, biphasic coarse dispersion [32].

Advantages of Suspension

1. Improves chemical stability of the drug
2. Masks the unpleasant/ bitter taste of drug

Liposomes

Liposomes are bilayered vesicle, in which aqueous compartment is covered by lipids. Phospholipids (as bilayer former) and cholesterol (as fluidity buffer) are essential components of liposomes [25, 27, 32].

Advantages of Liposomes

1. Deliver both hydrophilic as well as hydrophobic drugs.
2. Tissue sensitivity and toxicity are reduced.

Niosomes

Niosomes are bilayered vesicle in which aqueous compartment is covered by one or more non-ionic surfactant.

Advantages of Niosomes

1. More stable than liposomes.
2. More flexible in design and structure than liposomes.

Transfersomes

Transfersomes are complex vesicle in which aqueous compartment is covered by lipid bilayer in aqueous environment with a bilayer softening agent, which increase the flexibility and permeability of lipid bilayer [7, 34].

Advantages of Transfersomes

1. Penetrate through the narrow pores of skin without measurable loss.
2. Protect the encapsulated drug from enzymatic, metabolic degradation.

Aquasomes

Aquasomes (water bodies) are nanoparticulate carrier system [32, 35]. Advantages of aquasomes are; avoidance of reticuloendothelial clearance or degradation by other environmental challenges.

Colloidosomes

Colloidosomes are hollow shell microcapsules in which colloidal particles are assembled at the interface of two immiscible liquid phase [36].

Advantages of Colloidosomes

1. Good mechanical strength.
2. Biomolecules and cells can be easily encapsulated.

Sphingosomes

Sphingosomes are bilayered vesicle in which aqueous compartment is covered by sphingolipids. In order to increase the stability of liposomes, sphingosomes are developed by changing the outer most layer of natural or

synthetic lipids (phospholipid) by sphingolipids [32, 37].

Advantages of Sphingosomes

1. Better drug retention
2. Increased stability than liposomes
3. Reduced toxicity
4. Selective passive targeting of tumour tissue

Ufasomes

Ufasomes are suspension of closed lipid bilayer composed of unsaturated fatty acids and ionic surfactants [32, 38].

Advantages of Ufasomes

1. More stable than liposomes
2. Better entrapment efficiency for both hydrophilic and hydrophobic drugs
3. Cheaper than liposomes

Future Prospective of Novel Drug Delivery for Herbal Bioactive Molecules

Nowadays, people are opting herbal base medications as well as nutraceuticals for the treatment of diseases due to its lesser adverse effects, better therapeutic efficacy, lesser dose frequency. But it requires a novel drug delivery and targeting system for the herbal molecules. Several other novel drug delivery systems can be used to enhance the efficacy of drugs. The herbal based formulation can be issued in the Sublingual delivery because it bypasses the first phase of metabolism. Muco - adhesive drug delivery can also be used for targeted delivery of drugs which increases the bioavailability and minimizes the dose, toxicity and adverse reactions. Injectable hydrogel system with herbal bioactive molecules can be injected for local and sustained delivery of the therapeutics.

Overcoming the Limitations of Traditional Herbal Formulations/ Delivery System

There are certain limitations of traditional delivery systems that can overcome by the use of novel drug delivery system.

1) Large molecular size, lipid solubility, degradation in the acidic stomach are certain problems which limit the therapeutic activity of herbal extracts *in vivo* through these possess excellent bioactivity *in vitro*.
2) The novel drug delivery system is implicated to improve bioavailability of herbal bioactive molecules by increasing the solubility and permeability at the same time decreasing side, adverse effects.
3) A number of herbal bioactive molecules such as alkaloids, glycosides, terpenoids flavonoids, tannins, etc. showed enhanced therapeutic and pharmacological activity at similar or lesser dose when incorporated into novel drug delivery formulations as compared to conventional herbal formulations. Hence, the development of novel drug delivery system of herbal bioactive molecule offers effective and inexpensive formulations, well accepted as industrial scale production.

CONCLUSION

Numerous herbal bioactive molecules obtained from the plant kingdom possess numerous pharmacological activities against different kinds of pathophysiological abnormalities or illnesses. These herbal bioactive molecules are ineffective when directly used as therapeutic molecule because of certain physiochemical limitations of conventional drug delivery system such as lesser solubility, permeability, non-targeted organ delivery, metabolism, molecular size, acid degradation, hydrophilic-lipophilic valence, adverse effects and toxicity etc. Novel drug delivery systems of herbal bioactive molecule offers effective and inexpensive way of overcoming majority of the shortcomings of the conventional, traditional drug delivery system, hence should be widely accepted for large-scale industrial production to achieve better therapeutic efficiency.

ACKNOWLEDGMENT

We gratefully acknowledge ICMR-National Institute of Occupational Health, Ahmedabad & ICMR-National AIDS Research Institute, Pune for providing us condusive environment to write this review.

The review work did not required any funding support

CONFLICT OF INTEREST: Nil

COMPETING INTERESTS: None

SOURCE OF FUNDING: Nil

AUTHOR'S CONTRIBUTION

HariOm Singh: Overall supervision

Ranjana Choudhari: Manuscript writing, Native English corrections, Editing the figures and plagiarism check

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