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Review Article

MIRACULOUS THERAPEUTIC EFFECTS OF HERBAL DRUGS USING NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT
Plants are nature's remedies and have been used by human beings on earth since ancient times for food and medicine. Today there are global movements towards finding of herbal medicaments in plants on lab scale and after successive preclinical and clinical trial to bring them in market via a suitable drug delivery system for mankind. The basic thought behind it is treatment of each disease is hidden in nature. However, delivery of herbal drugs also requires modifications with the purpose to achieve sustained release, to increase patient compliance etc. Previously herbal drugs could not attract scientists towards the development of novel drug delivery systems due to processing, standardizing, extracting and identification difficulties. But now days with the advancement in the technology, novel drug delivery systems (NDDS) opens the door towards the development of herbal drug delivery systems. Novel drug delivery technologies have gained the importance to achieve modified delivery of herbal drugs thereby increasing the therapeutic value as well as reducing toxicity. For last one decade many novel carriers such as liposomes, nanoparticles, phytosomes and implants have been reported for successful modified delivery of various herbal drugs. The objective of this review article is to summarize various novel drug delivery technologies which have been developed for delivery of herbal drugs, to achieve better therapeutic response.
Key words: Nature, herbal, novel drug delivery system (NDDS).

INTRODUCTION

The method by which a drug is delivered can have a significant effect on its efficacy. An optimum amount of the concerned drug is administered to the patient in such a way that it reaches exactly the 'site of action' and produce therapeutic effects. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development[1]. Novel drug delivery system is a new approach to drug delivery. It helps the drug to act longer and more effectively. This overcomes limitations of old methods of drug administration. 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 the drug at molecular level.

Drawbacks of conventional dosage forms[2]

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which make attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever over medication occur.

Advantages of novel drug delivery systems

1. Enhancement of solubility.
2. Increased bioavailability.
3. Protection from toxicity.
4. Enhancement of pharmacological activity.
5. Enhancement of stability.
6. Improved tissue macrophages distribution.
7. Sustained delivery.
8. Protection from physical and chemical degradation.

Herbal drugs

"Herbal formulation mean a dosage form consisting of one or more herbs or processed herb(s) in specified quantities to provide specific nutritional, cosmetic benefits, and/or other benefits meant for use to diagnose treat, mitigate diseases of human beings or animals and/or to alter the structure or physiology of human beings or animals". Herbal preparations are obtained by subjecting whole plant, fragmented or cut plants, plants parts to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates[3].

Advantages of herbal drugs[4]

1. **Low risk of side effects:** Mostly herbal drugs are well tolerated by the patient, having fewer unintended consequences and fewer side effects than traditional medicine, and may be safer to use.
2. **More Effectiveness:** Herbal drugs are more effective for long-standing health complaints that don't respond well to traditional medicine. One example is the herbs and alternative remedies used to treat arthritis. Vioxx, a well-known prescription drug used to treat arthritis, was recalled due to increased risk of cardiovascular complications. Herbal treatments for arthritis, on the other hand, have lesser side effects. Such treatments include dietary changes like adding simple herbs, eliminating vegetables from the nightshade family and reducing white sugar consumption.
3. **Lower cost:** Cost of herbal drugs is much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription

medicines. Herbs tend to be inexpensive compared to drugs.

4. **Widespread availability:** Herbs are available without a prescription. Simple herbs, such as peppermint and chamomile, can be cultivated at home.

Limitation of herbal drugs[4]

1. **Not suitable for many diseases:** Modern medicine treats sudden and serious illnesses and accidents much more effectively than herbal or alternative treatments. An herbalist would not be able to treat serious trauma, such as a broken leg, nor would he be able to heal appendicitis or a heart attack as effectively as a conventional doctor using modern diagnostic tests, surgery, and drugs.
2. **Lack of dosage instructions:** Self treatment with herbal drugs may consist of many risk factors. Moreover with no proper direction of doses may lead to overdose.
3. **Poison risk associated with wild herbs:** Consumption of herbal drugs without correct identification of plant i.e. use of wrong part of plant may lead to poisoning.
4. **Lack of regulation:** Because herbal products are not strictly regulated, consumers may buy inferior quality herbs. The quality of herbal products may vary among batches, brands or manufacturers. This can make it much more difficult to prescribe the proper dose of an herb. All herbal drugs are not safe, some may be poisonous or may cause allergenic reactions.
5. **Longer duration of treatment-** Curing period is usually longer in comparison to conventional medication. Immense patience while undergoing herbal treatment is needed.

Importance of novel drug delivery systems for herbal drugs -Herbal drugs are becoming more popular in the modern world for their application to cure variety of diseases with less toxic effects and better therapeutic effects. There is a great possibility for herbal drugs that many compounds will be destroyed in the highly acidic pH of the stomach. Other components might be metabolized by the liver before reaching the blood. As a result, the actual amount of the drug may not reach the blood. If the drug doesn't reach the blood at a minimum level which is known as 'minimum effective level' then there will be no therapeutic effect. 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. Also for a long time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex polyherbal systems. 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[5]. Modern phytopharmaceutical research can solve the scientific needs (such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposome's, solid lipid nanoparticles and so on[6].

Drug delivery systems consisting of herbal drugs-Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone.

Liposomes

Liposomes are artificial microscopic vesicle (0.05-5.0 μm in diameter) consisting of an aqueous core enclosed in one or more phospholipids layers, used to convey vaccines, drugs, enzymes, or other substances to target cells or organs.

Li et al. prepared liposomes containing extracts of T. wilfordii thin-film dispersion method, the effect of process parameters and composition of materials on the entrapment efficiency of the main components were studied[7].

Advantages of liposome formulation

1. Hydrophobic and hydrophilic drug can be delivered.
2. Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene.
3. Sustained and controlled release of formulation can be possible.

Ethosomes

Ethosomes are vesicles composed of phospholipids and high concentration of ethanol. High concentration of ethanol in the vesicles led to enhancement in their permeability through the skin by fluidising the lipid domain of the skin. Zhou et al. developed a novel transmembrane pH gradient active loading method to prepare alkaloids binary ethosomes of sophora alopecuroides below the phase transition temperature of the phosphatidyl choline[8].

Advantages of ethosomal drug delivery

1. Transdermal permeation of drug through skin can be enhanced.
2. Large amounts of diverse groups of drugs can be delivered.
3. The ethosomal drug is administered in semisolid form, resulting in improved patient compliance[9].

Implants

These are the polymeric devices which are used for the controlled and sustained delivery of the drugs. These are directly placed in the body fluids/cavities and are fabricated by using biodegradable polymers. A microsurgery is always required for the insertion of these devices

Zhao et al. developed implants of the extract of danshen (Radix Salviae Miltiorrhizae) using the chitosan and gelatin[10].

Nanoparticles

Nanoparticles are the submicron size particles having size range 10 to 1000 nm. The main advantages of the nanoparticles are their stability and long term storage. The particle size and surface characteristics of nanoparticles can be easily modified for controlled and targeted drug delivery .Nano sizing led to increased solubility of components, reduction in the dose via improved absorption of active ingredient.

Yen et al. prepare C. chinensis nanoparticles by nanosuspension method and compare the hepatoprotective and antioxidant effects of C. chinensis ethanolic extract (CE) and CN on acetaminophen-induced hepatotoxicity in rats[11].

Advantages of herbal nanoparticle delivery system

1. Nanoparticulate system delivers the herbal formulation directly to the site of action.
2. Encapsulating drugs within nanoparticles can improve the solubility and pharmacokinetics of drugs.
3. Nanoparticles can also reach the choice of formulations, promote the drugs through the biological barriers and increase the bioavailability of drugs.
4. It can take the drug directly to the site of action without destroying surrounding environment.

Transferosomes

Transferosomes are phospholipid vesicles which act as potential carriers for the transdermal delivery of the drug as they overcome the difficulty of penetration through the stratum corneum and can easily penetrate through the intracellular pores of the skin due to their flexibility[12]. Increased penetration through stratum corneum results from hydration or osmotic force in the skin. Patel et al. prepared transferosomes containing the curcumin gel and an increase in the permeation was observed when compared with the simple gel through the skin[13].

Microemulsions

Microemulsions are the emulsions of O/W type having the size range of several microns. They are prepared by using the surfactants which are considered safe for the human use and approved by the FDA. These types of emulsions have higher surface area and hence can easily penetrate through the skin. They are also non toxic and non irritant in nature and can be used in the animals and veterinary purpose. Jing et al prepare the curcumin self-microemulsion, observe morphology and size diameter distribution of the microemulsion, and compare the absorption kinetics of curcumin microemulsion and micelle[14].

Advantages of emulsion-based formulations

1. Drug can be released for a long time because it is packed in the inner phase and makes direct contact with the body and other tissues.
2. As a result of the lipophilic drugs being made into o/w/o emulsion, the droplets of oil are phagocytosised by macrophages and increase its concentration in liver, spleen and kidney.
3. Emulsion contains herbal formulation, it will lead to increase in the stability of hydrolyzed formulated material and improve the penetrability of drug into skin and mucous. The new type, viz., elemenum emulsion, is used as an anti-cancer drug and causes no harm to the heart and liver[15].

Proniosomes

Proniosomes are dry formulations of surfactant coated carrier vesicles. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media[16].

In a study authors developed proniosomes of curcumin as a transdermal drug delivery system by encapsulating it in span 80, cholesterol, diethyl ether by ether injection method. The formulated systems were characterized for size, vesicle count, drug entrapment, angle of repose, rate of hydration, drug release profiles and vesicular stability at different storage conditions[17].

Advantages of proniosomes

1. More stable during storage and sterilization.
2. Easy to transfer and distribution.

Floating drug delivery system -Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Goindi et al. develop a multi-unit gastro-retentive floating dosage form of curcumin with targeted and sustained release characteristics[18].

The advantages of floating drug delivery system

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided. Better therapeutic effect of short half-life drugs can be achieved.
3. Gastric retention time is increased because of buoyancy.
4. Drug releases in controlled manner for prolonged period.
5. Site-specific drug delivery to stomach can be achieved.
6. Enhanced absorption of drugs which solubilise only in stomach.
7. No risk of dose dumping.
8. Avoidance of gastric irritation.

CONCLUSION

Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. 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. Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach. For a long time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex polyherbal systems. However, modern phytopharmaceutical research solves the scientific needs for herbal medicines as in modern medicine, which gives way for developing novel formulations such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles, and so on. An extensive research is going on in the area of novel drug delivery and targeting for plant actives and extracts. However, research in this area is still at the exploratory stage. Herbal drugs have enormous therapeutic potential which should be explored through some value added drug delivery systems.

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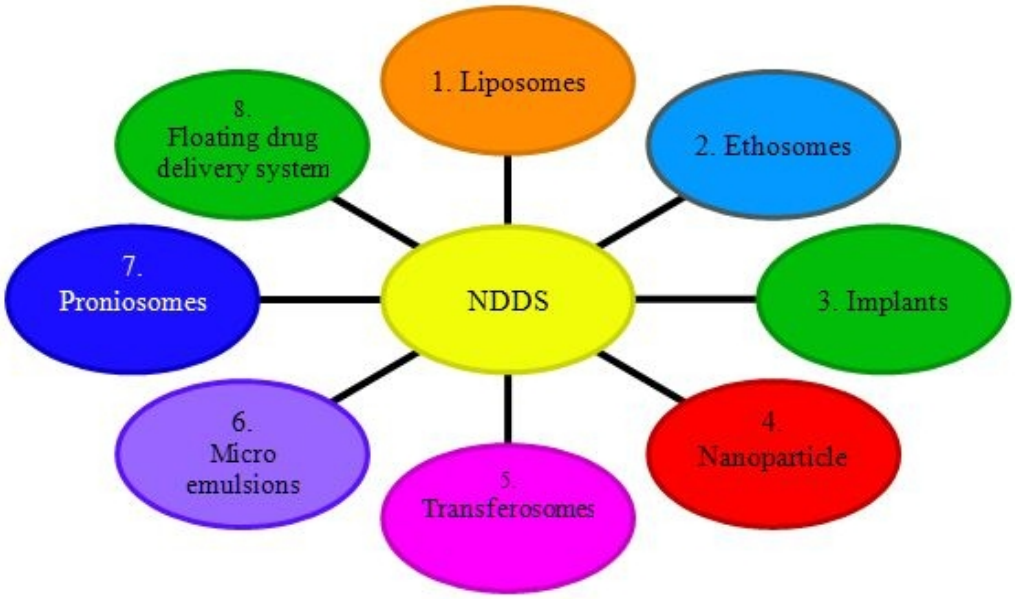

Figure: 1. Different novel drug delivery systems for herbal drugs.