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RECENT ADVANCES IN NOVEL HERBAL DRUG DELIVERY SYSTEM

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Abstract:

A novel drug delivery system is a new approach to drug delivery that overcomes the limitations of traditional drug delivery systems. Our country has a vast Ayurvedic knowledge base whose potential has only recently been realized. However, the drug delivery system used to administer the herbal medicine to the patient is outdated, resulting in reduced drug efficacy. If novel drug delivery technology is used in herbal medicine, it may improve the efficacy and reduce the side effects of various herbal compounds and herbs. Herbal formulations for novel drug delivery systems are more advantageous and beneficial than others. The use of herbal formulations containing liposomes, ethosomes, phytosomes, emulsions, microspheres, and solid lipid nanoparticles has improved the therapeutic effects of plant extracts. With the use of all of these, targeted delivery of the formulation is achieved, resulting in the formulation demonstrating effect on the site and increasing the formulation's bioavailability. This article attempts to cover different aspects related to the development of novel herbal formulations, biological activity and applications of novel formulations.

Keywords: Novel herbal drug delivery system, Herbal excipients, Current challenges, Applications.

1. Introduction

Many herbal drugs have been used safely and continuously in India's official recognised alternative health system for a very long time. Herbal therapy is an ancient science in the Indian medical system. Plant material is the main ingredient in traditional formulations[1]. Over the last few decades, much emphasis has been placed on the development of a novel drug delivery system (NDDS) for herbal drugs. Conventional dosage forms, including prolonged-release dosage forms, are unable to meet the requirements for both holding the drug component at a distinct rate as directed by the body's requirements. Developing nano-sized dosage forms (polymeric nanoparticles and nano capsules, liposomes, solid lipid nanoparticles, Phytosomes, and nano emulsion) has a number of advantages for herbal drugs, including increased solubility and bioavailability, protection from toxicity, increased pharmacological activity, increased stability, improved tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation. Thus, nano-sized NDDS of herbal drugs have a promising future for improving activity and overcoming issues associated with plant medicines.[2].

1.1 Necessity of NDDS in herbal drugs

1. The incorporation of novel drug delivery technique to herbal or plant actives reduces drug degradation or presystolic metabolism, as well as serious side effects caused by drug accumulation in nontargeted areas, and improves the ease of administration in paediatric and geriatric patients[3].
2. Conventional dosage forms, including prolonged release dosage forms, are incapable of meeting the ideal requirements of novel carriers, such as the ability to deliver the drug at a rate determined by the body's deficiency and to transmit the active entity of a herbal drug to the site of activity[4].
3. Many phytoconstituents, such as polyphenolics, have good water solubility but are poorly absorbed, either because of their multiple ring large sized particles, which cannot be absorbed by simple diffusion, or because of their poor miscibility with oil and other lipids, which severely limits their ability to cross the lipid rich outer membranes of the enterocytes[5]. Thus, nano-sized NDDSs of herbal drugs have a promising future for improving the natural process and alleviating the overwhelming problems associated with plant medicines.
4. Novel herbal drug carriers treat specific diseases by directing the drug only to the affected area of the patient's body[6].

1.2 Physiochemical properties of herbal drug[7]

Various physicochemical properties of herbal drugs are enlisted below:

1. Determination of moisture content
2. Solubility
3. Ash value
    a) Total ash value
    b) Acid in soluble ash
    c) Water soluble ash
    d) Sulphated ash

4. Specific Gravity
5. Viscosity
6. Melting point
7. Refractive index

1.3Advantages of NDDS in herbal drugs[8]

1. The addition of novel drug delivery technology to herbal phytoactives reduces the amount of drug degradation or pre-systemic metabolism as well as other side effects caused by drug accumulation in non-targeted areas, and it also makes administration simpler.
2. Delivering the herbal medication at a predetermined rate and delivering it to the area of action reduces toxic effects and increases bioavailability of the medication.
3. Contributes to improved tissue macrophage distribution, increased solubility, improved stability, protection from toxicity, increased pharmacological activity, sustained delivery, and protection from chemical and physical deterioration.
4. It might improve the effectiveness and lessen the negative effects of various herbal ingredients and herbs.
5. Some drugs have a range of optimal concentrations within which the greatest benefit can be obtained; concentrations outside of this range may be toxic or have no therapeutic benefit. Herbal novel drug delivery systems remove this restriction by delivering the right amount of drug in a controlled manner at a predetermined time.

1.4 Disadvantages NDDS in herbal drugs

1. Due to high cost of polymers and unavailability of specific polymers it is not an economical.
2. Failure of NDDS can result in dose dumping.
3. Termination of therapeutic effect with respect to NDDS tedious and complicated.
4. Limited drug choice for the development of NDDS.

1.5 Current challenges in upgrading and modernization of herbal formulations[9].

A key challenge is to objectively assess conflicting toxicological, epidemiological, and other data and the verification of herbal materials used. The following key issues remain. Management within ranges of risk

1. Standardization Safety, and efficacy assessment.
2. Evaluating “drug” interactions
3. Understanding why addition of harmful additives works
4. Communication of uncertainty
5. Pharmacological, toxicological, and clinical documentation
6. Pharmacovigilance
7. Constraints with clinical trials and people available

2. Approaches in novel herbal drug delivery system

The interdisciplinary approach of polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology is the foundation of novel drug delivery systems (NDDS)[10].

A. Liposomes[11]

A liposome is a bilayer, 25–2.5 nm-sized vesicular carrier system of phospholipids and cholesterol. Their capacity to encapsulate a variety of materials and their adaptability in terms of structure are their key advantages. Drugs with widely varying solubility or lipophilicity can be encapsulated in liposomes.

B. Phytosomes[12]

The majority of phytomedicines' bioactive components are flavonoids, which have a low oral bioavailability. Water-soluble phytoconstituent molecules (mainly polyphenols) can be converted into lipid compatible molecular complexes, which are called phytosomes. Due to their improved ability to cross lipid-rich bio membranes and ultimately reach the blood, phytosomes are more bioavailable than simple herbal extracts. To make phytoconstituents lipid compatible, phospholipids from soy, primarily phosphatidylcholine, are used as lipid-phase substances.

C. Niosomes[13-15]

Niosomes are a novel drug delivery system that entrap hydrophilic drugs in the core cavity and hydrophobic drugs in the non-polar region located within the bilayer, allowing for the incorporation of both hydrophilic and hydrophobic drugs. The niosomes are amphiphilic in nature; the name "niosomes" refers to the fact that the medication is enclosed in a vesicle made of a non-ionic surfactant. The size of niosomes is extremely small and microscopic.

D. Ethosomes

For many years, the vesicles' significance in cellular communication and particle transportation has been well understood. In order to improve drug delivery within their cavities and tag the vesicle for cell specificity, researchers have gained an understanding of the structure and properties of vesicles. The discovery of an Ethosome, a vesicle derivative, was one of the most important developments in vesicle research. They are primarily employed in the transdermal route of drug delivery. Ethosomes, which can be hydrophilic, lipophilic, or amphiphilic in their physicochemical properties, can entrap drugs[16]. Drugs are delivered using ethosomes, which are soft, malleable vesicles that can penetrate deep skin layers and/or the bloodstream. Ethosomes can range in size from nanometers to microns (µ)[17].

E. Transferosome

Gregor Ceve coined the term "transferosome" and the concept behind it in 1991. The Latin word transforre, which means to ‘carry across’, and the Greek word ‘soma’, which means "body," are the roots of the word same, which means "carrying body." An artificial vesicle that resembles the natural cell vesicle is called a Transfersome carrier. It is therefore suitable for controlled and targeted drug delivery. Transferosomes are a complex aggregate that is extremely adaptable and resilient to stress. It is a highly deformable vesicle with a complex lipid bilayer encasing an aqueous core. [18, 19]

F. Microsphere

Microspheres are solid, spherical, 1-1000µm in diameter particles. They are spherical, freely flowing particles made of synthetic polymers or proteins. There are two types of microspheres -

1. Microcapsules.
2. Micrometrics.

Microcapsules are those in which the substance that is being encapsulated is clearly surrounded by the capsule wall, as opposed to micrometrics, in which the substance is dispersed throughout the matrix of the microsphere. The potential for controlled drug release exists in solid biodegradable microspheres that incorporate a drug that has been dissolved or dispersed through the particle matrix.[20]

G. Microemulsion

A surfactant interfacial film, frequently in conjunction with a co-surfactant, stabilises microemulsions, which are defined as clear, transparent, thermodynamically stable dispersions of oil and water.[21] Hoar and Schulman, who developed a transparent, stable formulation by triturating a milky emulsion with hexanol and adding alcohol as a co-surfactant in the 1940s, introduced the idea of a microemulsion[22,23].

H. Nanoparticles

Both hydrophilic and hydrophobic drugs can be delivered effectively using nanoparticles. The size range of nanoparticles, which are submicron-sized particles, is 10 to 1000 nm[24]. Controlling particle size, surface properties, and release of pharmacologically active agents are the main objectives when designing nanoparticles as a delivery system in order to achieve the drug's site-specific action at the therapeutically ideal rate and dose regimen[25].

3. Herbal Excipients[26]

Pharmaceutical excipients are non-active ingredients that are combined with therapeutically active compounds to formulate the pharmaceutical substance. Many pharmaceutical excipients are derived from plants, including agar, alginate, starch, carrageen, guar gum, Xanthan gum, gelatine, pectin, acacia, tragacanth, and cellulose, which are used in the pharmaceutical industry as binding agents, disintegrates, protectives, cellulose, sustaining agent, thickening agent, base in suppositories, gelling agent, stabilizer, and coating agent.

3.1 Classification of herbal excipient[27]

A. Table No. 3.1: Classification according to their application and function in the drug

Sr.No.	Classification	Sr.No.	Classification
1.	Binder	**6.**	Disintegrants
2.	Diluents	**7.**	Polishing film-forming & coating agent
3.	Lubricants	**8.**	Plasticizers
4.	Colidants	**9.**	Suspending agent
5.	Colouring agent	**10.**	antioxidants & preservatives

B. Classification is based on the source

1. Marine origin/algal (seaweed) gums: agar, carrageenans, alginic acid, and laminarin;
2. Plant origin: Shrubs/tree exudates: gum arabic, gum ghatti, gum karaya, gum tragacanth, and khaya and albiziagums.
3. Seed gums: guar gum, locust bean gum, starch, amylose, andcellulose;
4. Extracts: pectin, larch gum;
5. Tuber and roots: potato starch;
6. Animal origin: chitin and chitosan, chondroitin sulphate, and hyaluronic acid;
7. Microbial origin (bacterial and fungal): xanthan, dextran, curdian, pullulan, zanflo, emulsion, Baker's yeast glycan, schizophyllan, lentinan, krestin, and scleroglucan

3.2 Advantage of herbal excipients[28]

1. Biodegradable
2. Safe and devoid of side effects
3. Easy availability
4. Biocompatible and non-toxic
5. Economic

3.3 Disadvantages of herbal excipients[29,30]

1. **Microbial contamination:** They are exposed to the external environment during production, which increases the possibility of microbial contamination.
2. **Variation:** Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, whereas natural polymer production is affected by the environment and various physical factors.
3. **The uncontrolled rate of hydration:** The percentage of chemical constituents present in a given substance may differ due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions.
4. **Slow Process:** Because the production rate is determined by the environment and many other factors, it cannot be altered. As a result, natural polymers build slowly.
5. **Heavy metal contamination:** Heavy metal contamination is frequently associated with herbal excipients.

4. Application of novel herbal drug delivery system[31]

Great advances have been made in the development of novel drug delivery systems (NDDS) for plant actives and extracts in recent years. Bioactive and plant extracts have been used to develop a variety of novel herbal formulations such as polymeric nanoparticles, Nanocapsules, liposomes, phytosomes, Nanoemulsions, microspheres, Transferosomes, and Ethosomes.

Table No.4.1: Liposomal herbal formulations.[32-35]

Formulation	Active ingredients	Application of liposome formulation	Biological activity	Route of Administration
Quercetin liposomes	Quercetin	Reduced dose, enhance penetration in blood brain barrier	Antioxidant	Intranasal
Liposome encapsulated silymarin	Silymarin	Improve bioavailability	hepatoprotective	Buccal

Catechins liposomes	Catechins	Increased permeation through skin	Antioxidant	Transdermal
Brovincamine liposomes	Brovincamine	Sustained delivery of breviscapine	Cardiovascular diseases	Intramuscular

Table No. 4.2 Nano structured herbal formulations.[36-40]

Formulation	**Active ingredients**	**Application of nanostructured formulations**	**Biological activity**	**Route of administration**
Nanoparticle of Cuscuta chinensis	Flavonoids and lignans	Improve water solubility	Hepatoprotective and antioxidant effects	Oral
Silibini-loaded nanoparticles	Silibini	High entrapment efficiency and stability	Hepatoprotective	-
Breviscapine-loaded Nanoparticles	Breviscapine	Prolong the half-life and decrease RES uptake	Cardiovascular	Intravenous
Naringenin-loaded Nanoparticles	Naringenin	improved the release of NAR and improved its solubility	Hepatoprotective	Oral

Table No. 4.3 Phytosomal herbal formulations.[41-43]

Formulations	**Active ingredients**	**Applications of phytosomal formulations**	**Biological activity**	**Route of administration**
Ginkgo Phytosome	Flavonoids	inhibits lipid peroxidation (LPO), stabilize the ROS	Hepatoprotective, antioxidant	Oral
Silybin Phytosome	Flavonoids	Absorption of Silybin phytosome from silybin is approximately seven times greater	Hepatoprotective, antioxidant for liver and skin	oral
Naringenin Phytosomes	Naringenin	Prolonged duration of action	Antioxidant activity	oral

Table No. 4.4 Emulsion herbal formulations.[44,45]

Formulation	Active ingredients	Applications of emulsion formulation	Biological activity	Route of administration
Silybin Nano emulsion	Silybin	Sustained release formulation	Hepatoprotective	Intramuscular
Quercetin micro-Emulsion	Quercetin	Enhance penetration into stratum corneum and epidermis	Antioxidant	Topical

Table No. 4.5 Microspheres encapsulated herbal formulations.[46,47]

Formulation	Active ingredients	Application of formulation	Biological activity	Route of administration
Zedoary oil Microsphere	Zedoary oil	Sustained release and Higher bioavailability	Hepatoprotective	Oral

5. Targeted herbal drug delivery system for cancer treatment[48]

Several novel drug delivery systems (NDDS) have been developed over the last two decades with the primary goal of improving medication bioavailability, minimising adverse effects, and preventing drug degradation. Other advantages of NDDS include increased solubility, improved bioavailability, fewer undesirable side effects, enhanced therapeutic action, improved stability, and improved drug distribution. It also includes pharmacokinetics, pharmacodynamics, and immunogenicity regulation. The advantage of NDDS is that it makes drug administration more convenient for patients[49-51]. Drugs are released from drug delivery systems through two mechanisms: passive targeting and active targeting. Passive targeting can be seen in the preservation of chemotherapeutic drugs in solid tumours, which results in increased tumour vascular permeability. Active targeting includes specific receptors on the cell's surface as well as ligand-receptor interactions[52]

5.1 Types of novel drugs delivery systems for herbal anti-cancer compounds

For the review of anticancer herbal nano formulations, recently published data is taken into consideration. NDDS come in many forms and contain a variety of ingredients. They are used to administer drugs to the body as well as to have additional pharmacokinetic and pharmacodynamic properties. Table 5.1 illustrates the various drug delivery systems for herbal anti-cancer substances.

Table No.5.1 Types of novel drug delivery systems for herbal anti-cancer compounds.

Novel Drug Delivery Systems (NDDS)	Phytochemicals	References
Biopolymer based nanocarrier (BBN)	Curcumin, Quercetin, Resveratrol, etc.	53,54
Liposomes	Liposomes Carotenoids, epigallocatechin gallate, Curcumin, Quercetin, Resveratrol, etc.	55-58
Niosomes	Thymoquinone, Curcumin, Quercetin, Resveratrol, etc.	59,60
Nanoemulsion	Paclitaxal, rutin, genistein, brucea javanica oil, and coixenolide, etc.	61-65
Polymeric nanoparticles	Curcumin, Quercetin, Resveratrol, etc.	66

6. Conclusion:

Since ancient times, herbal medicines have been used extensively around the world. A large population holds that these drugs have better therapeutic value than allopathic ones because they have fewer side effects. By incorporating Ayurvedic medicines into contemporary dosage forms, they can be used in a more ethical manner with increased efficacy. It is preferable to use herbal excipients because they not only perform their function in formulation but also provide health benefits by doing away with the issue of synthetic chemicals. When administered through a novel drug delivery system, standardized plant extracts or primarily polar phytoconstituents like flavonoids, terpenoids, tannins, and xanthones exhibit much better absorption profiles that allow them to cross the biological membrane, resulting in increased bioavailability. In contrast to the traditional plant extract or phytomolecule, more of the active constituent is present at the site of action (liver, brain, heart, kidney, etc.) at a similar or lower dose. As a result, the therapeutic effect is improved, more detectable, and lasts longer. Hence there is great potential in the development of novel drug delivery systems for plant actives and extracts.

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