



"NOVEL HERBAL DRUG DELIVERY SYSTEM, ITS ANALYTICAL ASPECT AND APPLICATIONS"

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Abstract

The kind of novel herbal formulations such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transfersomes, and ethosomes has been reported using proactive and plant selections. The novel formulations are described to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, and protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. Phytosome is a patented technology developed by a leading maker of drugs and nutraceuticals, to incorporate standardized plant extracts or water-soluble phytoconstituents into phospholipids to produce lipid-compatible molecular complexes. The herbal drugs can be used in a more upright course with enhanced efficacy by incorporating them into modern dosage forms. This can be accomplished by designing novel drug delivery

systems for herbal ingredients. The present review highlights the current condition of the development of novel herbal formulations and summarizes their type of active components, biological activity, and applications of novel formulations. **Keywords:** cancer, diabetes, Herbal medicines, herbal excipient, liposome, phytosome, transfersomes

Introduction

Necessity of NDDS in herbal drugs

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Modern medicine cures a particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Drug delivery system is the method by which 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 starts working then and there. Novel

drug delivery system attempts to eliminate all the disadvantages associated with conventional drug delivery systems. There are various approaches by which novel drug delivery can be achieved.^[1]

95% of all experimental drugs have low pharmacokinetic and biopharmaceutical properties at present. Consequently, suitable medication distribution schemes must only be established at the site without harming healthy bodies and tissues, which will disperse the therapeutically activated drug molecules, lower the efficacy doses as well as improve therapeutic indices and safety profiles in new therapists.^[2]

Physicochemical properties of herbal drug

The various physicochemical parameters that were determined as per The Unani Pharmacopeia of India include the following.

Description :It included evaluation of plant by colour, odour, taste, size, shape, and special feature, like touch, texture, and so forth.

Loss on Drying :10 g of plant material was placed (without preliminary drying) after accurately weighing it in a tarred evaporated dish. This was dried at 105°C for 5 h and weighed. Drying and weighing was continued at 1 h interval until we got the constant weight. Constant weight was reached when two consecutive weights, after drying for 30 min. and cooling for 30 min. in a desiccator, showed not more than 0.1 g difference.

Extractive Values (Successive) :A known amount of plant material was taken and all the sugars were leached out with cold water, dried thoroughly in a desiccator till weight was constant, and then extracted successively with petrol, EtOAc, MeOH, and water in a Soxhlet extractor for complete extraction and different extracts were weighed quantitatively and percentage with respect to the weight of the plant material taken was calculated.^[3]

Biological properties of herbal drug

The herbal drug has various biological properties are as follows

Cancer, Cardiovascular Diseases, Arthritis, Alzheimers Disease, Cataracts, Diabetes, Anti-Inflammatory, Antimicrobial, Cardioprotective, Neurodegenerative Disorders, Digestive Disorders, Antimutagenic, Antioxidant, Diabetic Nephropathy, Lowers Bad Cholesterol, Cardio Vascular Diseases, Anti Arrhythmic, Hypolipedemic, Antithrombotic, Asthma, Dysmenorrhea, Diabetes, Gastrointestinal Disorders, Constipation, Toxin Neutralisation^[4]

Advantages of novel herbal drug delivery system

1. They are site-specific, biodegradable, non-toxic and store for at least a year.
2. You may target a drug to a particular position in the body by adding targeted ligands to particle surfaces or by using magnetic guidance.
3. The system can be used on different routes such as oral, nasal, maternal, intraocular, etc.
4. Nanoparticles can easily be manipulated to achieve both passive and active drug targets following parenteral administration, particle size and surface characteristics.^[2]

Current challenges in upgrading and modernization of herbal formulations

1. **Quality issues:** Adulteration, misidentification of plant, faulty collection and preparation, incorrect formulation process are the main problems that reduces the effectiveness of herbal preparation and can be considered as key factors affecting quality and purity of herbal medicines.
2. **Processing and harvesting issues:** Indiscriminate harvesting, poor agriculture and propagation method, poor pre and post harvest practices, lack of processing techniques leads to the substandard quality of herbal drugs.

3. Administrative issues: Lack of regulation and controlling authority in herbal sector, lack of proper monitoring and controlling are absolute need for the quality of drugs.

4. Infrastructure related issue: Lack of processing technique, trained personal, sophisticated instrument, utilization of modern techniques, facility to fabricate instrument locally are the major problems.

5. Pharmacovigilance: Proper pharmacovigilance in herbal sector is the need of time to find the toxicological data and adverse drug reaction of herbal drugs. Adverse reactions, contraindications, interactions with other drug, food and existing orthodox pharmaceuticals need to be monitored properly.

6. Clinical trial: Since the safety continues to be a foremost issue with the use of herbal remedies therefore, clinical trials are necessary to understand the safety and efficacy of these drugs before introducing them in global market.^[5]

Approaches in novel herbal drug delivery systems

Types of novel herbal formulations

- Liposomes
- Phytosomes
- Niosomes
- Ethosomes
- Transferosomes
- Microsphere
- Microemulsion
- Nanoparticles

● Liposomes

Introduction

The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse (float) into their interior.

Liposomes are condensed bilayered vesicles with a completely contained aqueous volume. A lipid membrane bilayer consisting mainly of natural or synthetic phospholipids. The name comes from two Greek words: "Lipos" which means fat, "Soma" The flesh.^[2]

Methods of liposome preparation

All the methods of preparing the liposomes involve four basic stages:

1. Drying down lipids from organic solvent.
2. Dispersing the lipid in aqueous media
3. Purifying the resultant liposome.
4. Analyzing the final product.

Method of liposome preparation and drug loading

The following methods are used for the preparation of liposome:

1. Passive loading techniques
2. Active loading technique.^[6]

Advantages of Liposome

1. Provides selective passive targeting to tumor tissues (Liposomal doxorubicin).
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Reduction in toxicity of the encapsulated agents.
5. Site avoidance effect.
6. Flexibility to couple with site specific ligands to achieve active^[2]

Disadvantages of liposome

1. Low solubility
2. Short half-life

3. Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction
4. Leakage and fusion of encapsulated drug/molecules
5. Production cost is high
6. Fewer stables^[6]

● Phytosomes

Introduction

In phytosomes, the complexation of phospholipids and water soluble active plant components involve chemical bond formation and therefore more stable. However in liposomes no chemical bond is formed and phosphatidylcholine molecules simply surround the water-soluble components. The phytosomes substantially improve the bioavailability of these hydrophilic active components. Phytosomes can easily cross the lipid membranes and are reported to increase the bioavailability of poorly lipid soluble plant based drugs by increasing the absorption in gastrointestinal tract.^[7]

Method of preparation

Accurately weighed quantity of phosphatidylcholine and cholesterol were dissolved in 10 ml of chloroform in a round bottom flask (RBF) and sonicated for 10 min using bath sonicator. Organic solvent removal is done by Rotary evaporator (45-50°C). After complete removal of solvent thin layer of phospholipids mixture was formed. This film was hydrated with methanolic extract of plant in rotary evaporator (37- 40°C for 1 hour). After hydration, mixture of lipid and plant extract was sonicated for 20 minutes in presence of ice bath for heat dissipation. Then prepared phytosomes were filled in amber colored bottle and stored in freezer (2-8 °C) until used^[8]

Advantages of Liposome

1. Giving synergistic effect when hepatoprotective substances are employed
2. Greater therapeutic benefit
3. Better stability profile
4. Appreciable drug entrapment
5. Reduced dose requirement^[7]

6. In Phytosome, chemical bonds are formed between phosphatidylcholine molecules, so it shows good stability.
7. Phytosome improves the percutaneous absorption of herbal phytoconstituents.^[9]

Disadvantages of Liposome

1. Despites of several advantages of phytosomes some fatal disadvantages such as phospholipids (lecithin) can induce proliferation on MCF-7 breast cancer cell line has been reported.
2. A major disadvantage of phytosome is leaching of the phytoconstituents off the 'some' which reduces the desired drug concentration indicating their unstable nature^[10]

● Niosomes

Introduction

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surfactants. Niosomes are mostly preferred than liposomes because they are stable and cost effective. Niosomes potentiate the pharmacological action of the drug molecules by delaying the clearance of the drug from the circulation, protecting the drug from biological environment and restricting the effects only to the target cells. In novel drug delivery it has applications on treatment of cancer, used as a carrier in haemoglobin, delivery of the peptide drugs through oral route, in treatment of leishmaniasis, in ophthalmic delivery and as carrier in dermal drug delivery

Methods of preparation

1. Hand shaking method (Thin film hydration technique).
2. Micro fluidisation.
3. Reverse Phase Evaporation (REV).
4. Ether Injection Method.

5. Trans-membrane pH-gradient (inside acidic).
6. The Bubble Method.
7. Sonication.
8. Multiple extrusion method.
9. Formation of niosomes from proniosomes.

Advantages of Niosome

1. Reduced side effects and shows maximum duration of action.
2. Patient compliance is more compared to other delivery system.
3. Quantity of drug used is very less for achieving its desired effect.
4. Act as depot formulation, thus the drug is released in a controlled manner.
5. Drug is protected from first pass metabolism and gastrointestinal degradation.
6. Possess stable structure even in emulsion form.
7. Niosomes are available in oral, topical as well as parenteral routes.

Disadvantages of Niosome

1. Time consuming process.
2. Specialized equipments are required for processing.
3. Physically unstable ^[11]

• Ethosomes

Introduction

Ethosomes were developed by Touitou et al., 1997, as additional novel lipid carriers composed of ethanol, phospholipids, and water. They are reported

to improve the skin delivery of various drugs. Ethanol is an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Ethosomes are soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water. These soft vesicles represent novel vesicles carriers for enhanced delivery through the skin. The size of the ethosomes vesicles can be modulated from tens of nanometers to microns.

Method of preparation

1. Hot method
2. Cold method

Advantages of ethosome

1. Ethosomes enhance permeation of the drug through skin transdermal and dermal delivery.
2. Ethosomes are platforms for the delivery of large and diverse groups of drugs (peptides, protein molecules).
3. Ethosomal systems are much more efficient at delivering a fluorescent probe (quantum dots) to the skin in terms of quantity and depth.
4. Various applications in the pharmaceutical, veterinary, and cosmetic fields^[12]

Disadvantages of Ethosome

1. Adhesive may not adhere well to all types of skin.
2. May not be economical.
3. Poor yield.
4. Loss of product during transfer from organic to water media.
5. The main advantage of ethosomes over liposomes is the increased permeation of the drug.^[13]

• Transferosomes

Introduction

Gregor Cevc introduced the definition and idea of transfersome in 1991. The Title is derived from the Latin word 'transferre' which means, "to carry" means "to transport" Through' and "soma" fora, the Greek term "body." A translator is an artificial carrier A vesicle similar to the normal vesicle of the cell. It is therefore suitable for managed and targeted Delivery of drugs. Transfersome is a dynamic aggregate that is highly adaptable, stress reactive. It is a deformable vesicle with an aqueous center surrounded by the complex Fat bilayer.^[2]

Method of preparation

1. Thin film hydration method
2. Modified Hand Shaking Lipid Film Hydration Method.^[14]

Advantages of transfersomes

1. Small constriction (5-10 times smaller) can be caused by transfers. Without observable loss, except their own diameter.
2. In the case of lipophilic medicine they have a high capture efficiency of about 90%.
3. This high deformity gives the intact vesicles a greater penetration.
4. Transfers have a hydrophobic and hydrophilic infrastructure Together and as a result, drug molecules with a wide variety of Solubility.
5. They function as a warehouse, slowly and steadily releasing their contents.^[2]

Disadvantages of transfersomes

1. Transfersomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.
3. Transfersomes formulations are expensive.^[15]

● Microsphere

Introduction

Drug delivery system target drug to the specific body site which having enormous impact on the healthcare system¹⁻³. The ideal drug delivery system delivers the drug at rate decided by need of body throughout the period of treatment therefore carrier technology find out the intelligent approach for drug delivery by coupling the drug to carrier particles example, microspheres, nanoparticles, liposomes⁴⁻⁶ oral route of drug administration is most preferable route for taking medication. Microspheres are small spherical particles which having diameter 1um to 100um. they are free flowing particles which are consisting of proteins or synthetic polymers this are biodegradable in nature.^[16]

Method of preparation

1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction
8. Quassi emulsion solvent diffusion.^[16]

Advantages of microspheres

1. They provide protection before after administration for unstable drug.
2. They reduced concentration of drug at site other than the tissue or the target organ.
3. Decrease dose and toxicity.
4. Particle size reduction for enhancing solubility of poorly soluble drugs.
5. Provide constant and prolonged therapeutic effect.^[16]

Disadvantages of microspheres

1. The fate of polymer matrix and its effect on the environment.
2. There are differences in release from one to another dosage form.
3. Any loss of integrity in release pattern may cause potential toxicity.

4. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
5. Reproducibility is less.
6. Low drug loading is done in case of parental microspheres.^[17]

2. Same microemulsions have the ability to carry both lipophilic and hydrophilic drugs.
3. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

● Microemulsion

Introduction

Microemulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o).

Method of preparation

The drug is dissolved in the lipophilic part of the microemulsion i.e. oil and the water phases can be combined with surfactant and then cosurfactant is added at slow rate with constant stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated is determined with the help of pseudoternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then allowed to equilibrate. Gel may be prepared by adding a gelling agent to the above microemulsion. Carbomers (crosslinked polyacrylic acid polymers) are the most widely used gelling agent.

Advantages of microemulsion

1. Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system.

Disadvantages of Microemulsion

1. Use of a large concentration of surfactant and co-surfactant is necessary for stabilizing the droplets of microemulsion.
2. Limited solubilizing capacity for high-melting substances used in the system.
3. The surfactant should be nontoxic for use in pharmaceutical applications.
4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change as microemulsion delivered to patients.^[18]

● Nanoparticles

Introduction

The prefix "nano" has found in last decade an ever-increasing application to different fields of the knowledge. Nanoscience, nanotechnology, nanomaterials or nanochemistry are only a few of the new nano-containing terms that occur frequently in scientific reports, in popular books as well as in newspapers and that have become familiar to a wide public, even of non-experts. The prefix comes from the ancient Greek νᾶνος through the Latin nanus meaning literally dwarf and by extension, very small. Within the convention of International System of Units (SI) it is used to indicate a reduction factor of 10⁹ times. So, the nanosized world is typically measured in nanometers (1nm corresponding to 10⁻⁹ m) and it encompasses systems whose size is above molecular dimensions and below macroscopic ones (generally > 1 nm and < 100 nm).^[19]

Method of preparation

- A. Mechanical Methods

- 1) High Energy Ball Milling
- 2) Melt Mixing
- B. Methods Based on Evaporation
 - 1) Physical Vapour Deposition
 - 2) Laser Ablation
- C. Chemical Methods
 - 1) Colloids synthesis
 - 2) Synthesis of Metal Nanoparticles by Colloidal Method
 - 3) Sol-Gel Method
- D. Biological Methods
 - 1) Synthesis using Plant Extracts
 - 2) Synthesis using DNA.^[19]

Advantages of Nanoparticles

1. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
2. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
3. Liposomes and polymer based nanoparticulates are generally biodegradable, do not accumulate in the body and so are possibly risk free.
4. Small sized nanoparticles can penetrate through smaller capillaries, which could allow efficient drug accumulation at the target sites.
5. Various routes of administration are available including oral, nasal, parenteral, intra-ocular etc.

Disadvantages of Nanoparticles

1. Smaller the particles size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.
2. Small particles size results in limited drug loading and burst release. These practical problems have to be sorted out before nanoparticles can be used clinically or made commercially available.^[18]

Herbal excipients

Introduction to excipients

Pharmaceutical excipients are defined as a non-active ingredient which is used with therapeutically active compound to formulate the pharmaceutical substance. These affect the quality and efficacy of the drug more & more performance & functionally. The alternation of active ingredients, excipients, and processes are clear components for the product alternation. Many pharmaceutical excipients are obtained from plant origin such as Agar, Alginate, Starch, Carrageen a guar gum, Xanthan gum, Gelatin, Pectin, Acacia, Tragacanth, & Cellulose found in the pharmaceutical industry as Binding agent, Disintegrates, Protectives, cellulose, Sustaining agent, thickening agent, Base in suppositories, gelling agent, stabilizer & coating agent.

Classification of herbal excipient

Classification according to their application and function in the drug

- Binder
- Diluents
- Lubricants
- Colidants
- Disintegrants
- Polishing film-forming & coating agent
- Plasticizers
- Coloring agent
- Suspending agent
- preservatives
- antioxidants etc.

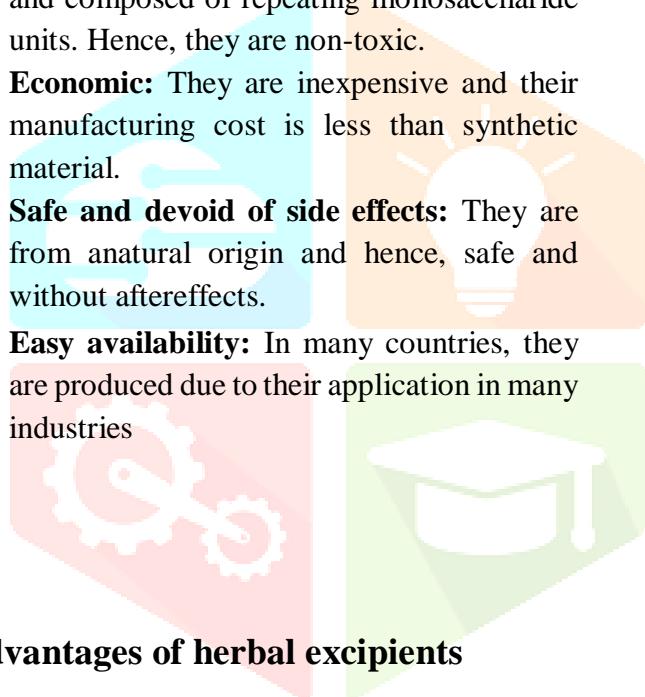
Classification is based on source

- **Marine origin/algal (seaweed) gums:** agar, carrageenans, alginic acid, and laminarin;
- **Plant origin: Shrubs/tree exudates:** gum arabic, gum ghatti, gum karaya, gum tragacanth, and khaya and albizia gums.
- **Seed gums:** guar gum, locust bean gum, starch, amylose, and cellulose;
- **Extracts:** pectin, larchgum;
- **Tuber and roots:** potato starch;
- **Animal origin:** chitin and chitosan, chondroitin sulfate, and hyaluronic acid;

- **Microbial origin (bacterial and fungal):** xanthan, dextran, curdian, pullulan, zanflo, emulsion, Baker's yeast glycan, schizophyllan, lentinan, krestin, and scleroglucan.

Advantages of herbal excipients

1. **Biodegradable:** Naturally occurring polymers produced by all living organisms. They show no adverse effects on the environment or human beings.
2. **Biocompatible and non-toxic:** Synthetically, all most all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence, they are non-toxic.
3. **Economic:** They are inexpensive and their manufacturing cost is less than synthetic material.
4. **Safe and devoid of side effects:** They are from anatural origin and hence, safe and without aftereffects.
5. **Easy availability:** In many countries, they are produced due to their application in many industries



Disadvantages of herbal excipients

1. **Microbial contamination** – During production, they are exposed to the external environment, and hence, there are chances of microbial contamination.
2. **Variation** – Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients while the production of natural polymers is dependent on the environment and various physical factors.
3. **The uncontrolled rate of hydration**– Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical

constituents existing in a given substance may differ.

4. **Slow Process**– As the production rate depends upon the environment and many other factors, it can't be changed. So natural polymers have a slow rate of construction.
5. **Heavy metal contamination**– There are chances of Heavy metal contamination often associated with herbal excipients.^[21]

Applications of herbal excipients

- **Locust bean gum** : Locust Bean Gum (LBG) (also known as Carob Gum) is obtained from the refined endosperm of seeds from the carob tree Ceretonia siliqua L. It is an evergreen tree of the legume family. Carob bean gum is obtained by removing and processing the endosperm from seeds of the carob tree .
- **Honey locust gum** : It is known botanically as Gleditsia triacanthos, and belongs to the order Leguminosea (suborder Mimosae). The gum is obtained from the seeds.
- **Khaya gum** : Khaya gum is a polysaccharide obtained from the incised trunk of the tree Khaya grandifoliola (family Meliaceae). The fact that the gum is naturally available, inexpensive and non-toxic has also fostered the interest in developing the gum for pharmaceutical use. Further work has also shown its potential as a directly compressible matrix system in the formulation of 61 controlled release tablets.
- **Aloe mucilage** : It is obtained from the leaves of Aloe barbadensis Miller. The aloe parenchyma tissue or pulp has been shown to contain proteins, lipids, amino acids, vitamins, enzymes, inorganic compounds and small organic compounds in addition to the different carbohydrates. Many investigators have identified partially acetylated mannan (or acemannan) as the primary polysaccharide of the gel, while

others found pectic substance as the primary polysaccharide.

- **Hakea Gum :** Hakea gum a dried exudates from the plant Hakea gibbosa family Proteaceae. Gums that are acidic arabinogalactans (type A). Molar proportions (%) of sugar constituents Glucuronic acid, Galactose, Arabinose, Mannose, Xylose is 12:43:32:5:8.
- **Pectin :** Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. In the food industry, folic acid incorporated microcapsules were prepared using alginate and combinations of alginate and pectin polymers so as to improve stability of folic acid. The blended alginate and pectin polymer matrix increased the folic acid encapsulation efficiency and reduced leakage from the capsules as compared to those made with alginate alone; they showed higher folic acid retention after freeze drying and storage.
- **Alginates :** Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. Alginates offer various applications in drug de-livery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications. [22]

Analytical aspect of novel herbal formulation

Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

Particle size and Zeta potential

The particle size and zeta potential can be determined by dynamic light scattering (DLS)

using a computerized inspection system and photon correlation spectroscopy (PCS). [23]

Drug Entrapment Efficiency

Weigh amount of microsphere are taken and crushed. Then in buffer solution it is dissolved with the help of stirrer. After stirring filtered it. The filtrate is analyses by UV spectrophotometer at particular wavelength by using calibration curve. Drug Entrapment efficiency is analyses by actual weight of microspheres / the theoretical weight of drug and polymer $\times 100$. [24]

Transition temperature

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry.

Surface tension activity measurement

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

Vesicle stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM.

Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method. [23]

In-vitro drug release study by dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements Paddle and basket.

Dissolution medium used for the study varies from 100-500 ml and speed of rotation from 50-100rpm. [17]

Excipient comparability study

Isothermal stress testing method is used to assess the compatibility of drug-drug/drug-excipient. [25]

Spectroscopic evaluations

To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used.

Fourier Transform Infrared (FTIR)

FTIR spectroscopy studies The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.

¹³C-NMR

In the ¹³C-NMR spectrum of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine, particularly when recorded in C6D6 at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60°, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.^[23]

Chromatographic analysis

Chemical fingerprints obtained by chromatographic technique and especially by hyphenated chromatography, are strongly recommended for the purpose of quality control of herbal medicines, since they might represent appropriately the “chemical

integrities” of the herbal medicines and therefore be used for authentication and identification of the herbal products. Thin layer chromatography (TLC) and High Performance Thin Layer Chromatography (HPTLC) are valuable tools for qualitative determination of small amounts of impurities. Also many analytical techniques such as Volumetric Analysis, Gravimetric Determinations, and Gas Chromatography (GC), Column Chromatography (CC), High Performance Liquid Chromatography (HPLC) and Spectrophotometric methods are also frequently used for quality control and standardization.^[26]

Applications of novel herbal drug delivery system

Diabetes

Due to the challenges of pharmacological therapy faced and the superiorities of nanoparticles (NPs) in drug delivery and imaging (Rai et al., 2016), researches have put increasing interest in nano carriers in the treatment and management of diabetes mellitus. The composition of systems for drug delivery mainly includes liposome, polymer-based NPs, and inorganic NPs. Among them, diverse polymer-based NPs including nanospheres, nanocapsules, micelles, and dendrimers are developed as suitable drug carriers. Table 1 contains several types of nano carriers used for loading insulin and other antidiabetic drugs, and summarizes their reported effects in vivo. These nano carriers have been found to be potentially beneficial in many aspects, such as protecting drugs from enzymatic degradation, improving their stability, overcoming different biological barriers in vivo, and increasing bioavailability. They could also act as an intelligent automatized system to mimic endogenous insulin delivery and possess a non-linear response to an external signal, which reduces the risk of hypoglycemia and obtain better compliance of patients. Moreover, they have great performance in more precisely delivering drugs to the targeted sites and sustaining and controlled release of drugs within targeted sites over a long period, which could minimize the undesirable side-effects and maximize

the therapeutic effect (Wang J. Q. et al., 2019). Otherwise, quantum dots and metal-oxide NPs are widely applied to the detection of pH and chemical analytes and imaging in drug delivery because of their unique photoluminescent properties. At the same time, the properties of polymer materials, the mean particle size and polydispersity, the surface electrical charge and hydrophilicity of nanoparticles are crucial for the delivery of antidiabetic drugs (Souto et al., 2019). Therefore, it is quite necessary and significant to develop appropriate NP delivery systems for effective diabetes treatment.^[27]

Hepatoprotective

Silymarin is a polyphenolic flavonoid isolated from seeds of the milk thistle *Silybum marianum* (Family Asteraceae). It has been used to treat liver and gallbladder disorders, including hepatitis, cirrhosis, and jaundice, and to protect the liver against poisoning from chemical and environmental toxins, including snake bites, insect stings, *Amanita phalloides* mushroom poisoning, and alcohol. Silymarin has also been reported to provide liver protection against CCl₄ and paracetamol-induced liver damage in rat models. Silymarin's effects are accomplished via several mechanisms. It prevents lipid peroxidation, protects the cell membrane from radical-induced damage, blocks the uptake of toxins such as *Amanita phalloides* toxin and stimulates ribosomal RNA polymerase thereby increases protein synthesis. Other mechanisms include anti-inflammation, antifibrosis and anticarcinogenesis. Silymarin absorption rate levels vary between 20 and 50%. Several reasons have been attributed for this poor bioavailability, e.g., poor enteral absorption, degradation by gastric fluid or its poor solubility. Several pharmaceutical approaches have been employed to improve the bioavailability of silymarin. These approaches include complexation of silymarin with phosphatidylcholine (Siliphos), complexation with cyclodextrins, complexation with phospholipids, provision of silymarin in the form of salts of polyhydroxyphenyl chromanones and othermore.^[28]

Cardiovascular disorder

Nanoparticles

Nanoparticles are the nano-sized particles used in the targeted drug delivery through the encapsulation process. Even though these nanoparticles show some toxic effects the polymeric nanoparticles are used in the treatment of acute myocardial infarction, which is caused due to atherosclerotic plaque destabilization and rupture by inflamed monocytes and macrophages. Some other examples of Nano drug delivery systems are PEG gold Nanoparticles, and Nanoparticles containing pitavastatin reduces the inflammation.

Drug-eluting Balloons

Drug-eluting balloons are used in the treatment of coronary restenosis, subsequent revascularization. The paclitaxel drug-eluting balloon is an important device that is used to deliver the antirestenotic drug paclitaxel into a coronary vessel. These eluting drug balloons are used as an alternative to eluting drug stents affected coronary artery drug-eluting balloon in the artery treated coronary artery by DEB.^[29]

Conclusion

Herbal medications have been widely employed all over the globe since ancient times and have been acknowledged by doctors and patients for their better therapeutic value as they cause fewer adverse effects as compared with modern medications. The drugs of Ayurvedic origin can be utilized in a more upright course with enhanced efficacy by incorporating in modern dosage forms. However, phytotherapeutics need a scientific approach to render the components in a new way to increase patient compliance and avoid repeated administration. This can be accomplished by designing NDDS for herbal ingredients. NDDS not only reduce the repeated administration to overcome noncompliance, 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. The novel research can also aid in capturing as well as to remain in the market. But there are many challenges with herbal drugs which need to be overcome like difficulty of conducting clinical research in herbal drugs, development of simple bioassays for biological standardization, pharmacological and toxicological evaluation methods' development, investigation of their sites of absorption, toxic herbal drugs in use, discovering various animal models for toxicity and safety evaluation, legal and regulatory aspects of herbal drugs and so on.



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