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NOVEL DRUG DELIVERY SYSTEMS: AN OVERVIEW

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ABSTRACT

Anciently plants are the basic ingredients used as natural remedies for food and medicines. Now global movements are taken for finding the herbal beneficial in plants as a medicament to bring them in market via a suitable drug delivery system for mankind. The basic aim behind this globalization is to treat each disease through herbal approach. However, delivery of herbal drugs also requires modification with the purpose to achieve sustain release, to increase patient compliance etc. previously herbal drugs could not attract scientists towards the modifications of novel drug delivery systems due to processing, standardizing, extracting and identification difficulties. But in today‟s era with the advancement in the technology, novel drug delivery systems (NDDS) approach towards the enhancement of herbal novel drug delivery system. With these advance techniques- protection from toxicity, enhancement in stability, improved bioavailability of herbal medicaments, and protection from physical and chemical degradation can be achieved. Novel drug delivery technologies have advantages in achieving modified delivery of herbal drugs by enhancing the therapeutic value as well as deducing toxicity. Presently, all reviews gives information regarding different novel approaches used for improving safety and efficacy of phytomedicines and application of herbal formulations. The main focus for the development of such delivery systems is for minimized drug degradation and loss, preventing harmful side effects and increased bioavailability. The ability to direct the drug loaded system to the site of interest is known as TARGETING. There are different drug carriers named as soluble polymers, micro particles made up of insoluble (or) biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes and micelles. Two major mechanisms can be distinguished for addressing the desired sites for drug release, (a) Passive and (b) Active targeting. The

controlled drug carrier systems categorized as micellar solutions, vesicles and liquid crystal dispersions as well as nanoparticle dispersions consisting of small particles of 10 – 400 nm offers great promise as drug delivery systems. Hydrogels are three dimensional hydrophilic polymer networks capable of imbibing large amounts of water or biological fluids.

KEYWORDS: New drug delivery system, Phytosome, Nanoparticles, Microsphere, Transdermal Drug Delivery System Carriers, Colloidal drug carriers.

INTRODUCTION

Dosage forms that consists one or more herbs or processed herbs in specified quantities to provide specific nutritional and cosmetic benefits are called HERBAL FORMULATIONS. Herbal preparations are obtained by subjecting whole plant, fragmented or cut plants, plant's parts for the treatments such as distillation, extraction, expression, fractionation, purification, concentration or fermentation. They include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.[1] Plant formulations itself has complex structure of many active constituents; as they provide synergistic action and increases the therapeutic value.[2] Herbal medicaments have lesser side effects.[3,4]

Physical and biochemical mechanisms are the key basis of NOVEL DRUG DELIVERY SYSTEM. Physical mechanisms also referred as 'Controlled Drug Delivery Systems' that include osmosis, diffusion, erosion, dissolution and electro transport. While biochemical mechanisms include monoclonal antibodies, gene therapy, vector systems, polymer drug adducts and liposomes. Targeting is the ability to direct the drug-loaded system to the site of interest.

Optimization of duration of action of drug, decreased dosage frequency, controlled site of release and maintained constant drug levels are the therapeutic benefits of novel drug delivery systems.[5,6,7]

Merits of Novel Drug Delivery System

1. Protection from physical and chemical degradation.
2. Sustainable delivery.
3. Improved tissue macrophages distribution.
4. Increased stability.
5. Increased pharmacological activity.

6. Protection from toxicity.
7. Increased bioavailability.
8. Increased solubility.[8]

Recent Developments In Novel Drug Delivery System of Herbals

1. Phytosome
2. Liposome
3. Nanoparticles
4. Emulsions
5. Microsphere
6. Ethosome
7. Solid lipid nanoparticles
8. Niosomes
9. Proniosomes
10. Transdermal Drug Delivery System
11. Dendrimers
12. Liquid Crystals
13. Hydrogels.[9]

1. PHYTOSOMES

They are lipid compatible molecular complex which are composed of "phyto" means plant and "some" means cell-like.[10] Complex of polyphenol phytoconstituents in the molar ratio with phosphatidyl choline turned into a new herbal drug delivery system, known as "Phytosome". They are advanced forms of herbal products that have better absorbed quality, utilized to produce better results as compared to that of conventional herbal extracts. On the aspect of pharmacokinetic and therapeutic profiles phytosomes have better adaptability than conventional herbal extracts.[11]

Advantages of Phytosomes

1. Size of the dose required is small due to enhanced absorption power of active constituents through phytosome.
2. Increased solubility of bile into herbal products and ability to target the liver due to enhanced entrapment of drugs.
3. Increased solubility due to formation of chemical bonds between the molecules of phosphotidyl choline.[12]

4. Improvement in the percutaneous absorption of herbal phytoconstituents.[13]

2. LIPOSOMES

Tiny pouches made up of lipid or fat molecules that surround the water core. These methods are widely used for clinical cancer treatment. Some different sorts of liposomes are also employed against infectious diseases and can deliver certain vaccines. During cancer treatment whole of the procedure carry out in certain steps are as follows, first the encapsulation of drugs then shielding of healthy cells to avoid toxicity and then preventing the concentration in vulnerable tissues like of patient's kidneys and liver. Liposomes have ability to reduce or eliminate certain common side effects of cancer treatment like that of nausea and hair loss.

Phospholipid bilayers are present in one or many in number as vesicles i. e, in the form of tiny pouch like structures. Polar drug molecule's encapsulation ensures the polar character of liposomal core. According, to the affinity regarding phospholipids they have the ability of solubilizing the amphiphilic and lipophilic molecules within the phospholipid bilayers.[14]

Advantages of liposomes

1. High biocompatibility.
2. Easy to prepare.
3. They are chemically versatile to allow the loading of hydrophilic, amphiphilic, and lipophilic compounds.
4. They have the ability of simple modulation for their pharmacokinetic properties by changing the chemical composition of the bilayer components.[15]

Use of Liposomes

The major use of LIPOSOME is to carry drugs at the site of action from the aspect of ongoing advancement in the field of Novel Drug Delivery System. Pharmacokinetic parameters of the drugs can be altered whether liposomes either in modified or unmodified forms. They are very much helpful in delivering the cytotoxic agents to the tumour tissue and preventing side effects like myelosuppression. There another use is to target receptor-mediated endocytosis. Modified liposomes also have huge applications in targeting various drugs to the organs like heart, liver, kidney, lungs and bones.[16]

3. NANOPARTICLE

Nanoparticles (including Nano spheres and Nano capsules) ranging from 10-200 nm in size.

They are present in solid state and are either amorphous or crystalline in nature. They have the ability to adsorb and/or encapsulate a drug, thus provide protection against chemical and enzymatic degradation. Presently, biodegradable polymeric nanoparticles offers great promise as enhanced potential drug delivery devices, in aspect of their applications in the controlled release of drugs, targeting particular organs / tissues, as carriers of DNA in gene therapy, and as the increased ability to deliver proteins, peptides and genes through the peroralroute.[17,18]

Advantages of herbal nanoparticle delivery system

1. Direct delivery of herbal formulation to the site of action can be achieved by Nano-particulate System.
2. Enhanced efficacy and therapeutic index.
3. Enhanced stability via encapsulation.
4. Improvised pharmacokinetic effect.
5. Can be produced with various sizes and compound surface properties.[19]

4. EMULSIONS

A biphasic system with one phase intimately dispersed in the other phase in the form of minute droplets in ranging from 0.1μm to 100 μm of diameter. Emulsion has one phase in water or aqueous medium, and the other one in oily or non-aqueous medium. Among them, the micro-emulsions are also known as Nano-emulsion, and the sub-micro-emulsion is called liquid emulsion.[20]

Micro-emulsion is based upon a principle which states that they are thermodynamically stable in combination with aco-surfactant.[21]

Advantages of emulsion-based formulations

1. They have the ability to release the drug for a long time due to inner phase packing of it.
2. Have contact with the body and other tissues.
3. As a result, the lipophilic drugs being made into o/w/o emulsion and the droplets of oil are phagocytosised by macrophages and which increases its concentration in liver, spleen and kidney.
4. Due to herbal formulation content present in emulsions they have increased stability of hydrolyzed formulated material and improved penetrability of drug into skin and mucous.
5. An emulsion used as an anti-cancer drug that causes no harm to the heart and liver named as

ELEMENUM.[22]

6. MICROSPHERES

They are comprised of small spherical particles, with diameters ranging typically from 1 μm to 1000 μm (1 mm). Microspheres are also referred to as micro-particles. Microsphere's manufacturing is possible from both natural and synthetic materials.

We also have some commercially available microspheres named as:

(1) Glass microspheres

(2) Polymer microspheres

(3) Ceramic microspheres.

Their classification is done as biodegradable or non-biodegradable. Biodegradable microspheres include albumin microspheres, modified starch microspheres, gelatin microspheres, polypropylene dextran microspheres, polylactic acid microspheres, etc. Current literature reports state that non-biodegradable microspheres include polylactic acid as the only polymer approved to be used by people, and it is used as a controlled-release agent. For different applications, solid and hollow microspheres are used that varies widely in density.[23]

7. ETHOSOMES

Mixtures of phospholipids and high concentration of ethanol gives rise to the formation of ETHOSOMES. To improve the delivery of drugs into deeper layer of skin and also in blood circulation their carriers are able to penetrate through the skin. These formulations are used to apply topically for delivering the alkaloids in the form of gel and cream for patients comfort. They do great job for increasing their permeability by fluidizing the lipid domain of the skin. The limitations of ethosomes for topical delivery are their unstable nature and poor skin penetration. The development of ethosomes was done for their ability of topical absorption of 'Tetrandrine' through dermal delivery, and for its relation formulations to the pharmacological activity of 'Tetrandrine' loaded in the formulation for the access. When drugs mixed in rat plasma it showed that tetrandine loaded Ethosomes when topically administered on rats the result of drug level was low and to be detected in rat plasma. Ethosomes were demonstrated as the most promising carrier for improved topical delivery of tentrandrine via skin.[24]

Advantages of ethosomal drug delivery

1. Ethosomes are able to enhance transdermal permeation of drug through skin.

2. Large amounts of diverse groups of drugs can be delivered easily with the help of ethosomes.
3. For improved patient's compliance Ethosomes drugs are available in semi- solid form when administered.[25]

8. SOLID LIPID NANOPARTICLES

A new pharmaceutical delivery system or pharmaceutical formulation is developed named as (SLNs).

The previous approaches were as follows- such as use of permeation enhancers, surface modification, pro-drug synthesis, complex formation and colloidal lipid carrier based strategies that have been developed for the delivery of drugs to intestinal lymphatic. In addition, polymeric nanoparticles, self-emulsifying delivery systems, liposomes, micro-emulsions, micellar solutions and recently solid lipid nanoparticles *(SLN)* have been exploited as probable possibilities as carriers for oral intestinal lymphatic delivery.[25]

The characteristics of solid lipid nanoparticle are typically such as spherical in shape with an average diameter between 10 and 1000 nm. They comprise a solid lipid core matrix which is able to solubilize lipophilic molecules.

Surfactants (emulsifiers) are used to stabilize the core of the solid lipid nanoparticles. Here the 'lipid' term is used in a broader sense and includes triglycerides (e.g. tristearin), di-glycerides (e.g. glycerolbahenate), mono- glycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetylpalmitate).To stabilize the lipid dispersion all classes of emulsifiers (with respect to charge and molecular weight) are used. To prevent particle agglomeration more efficiently combination of emulsifiers are proven to be effective.[26, 27]

9. NIOSOMES

A system with multi-lamellar vesicles formed from non-ionic surfactants of the alkyl or dialkylpolyglycerol ether class and cholesterol gives rise to the formation of NIO-SOMES. Previous studies, in association with L'Oreal have shown that, generally, niosome possesses properties of being potential drug carrier similar to liposomes. Niosomes are different from liposomes by offering certain advantages over liposomes.[28]

10. PRONIOSOMES

It is a sort of gel system which is step forward to niosome, which is utilized for various applications in delivering the actives at a desired site. Proniosomal gels are the formulations, which are converted from in situ hydration with water from the skin into niosomes.[29]

11. DENDRIMERS

The precisely defined synthetic nanoparticles which have approximate 5–10 nm of diameter are referred to as DENDRIMERS. They are composed in the form of layers of polymer that are surrounded by a central core. Different sites of action are present on the surface of the dendrimers to which drugs can be attached and also some sort of attachment sites for materials such as PEG which can be used to modify the way of dendrimer's to which it interacts with body are also present on them. To promote the body's defense mechanism and detecting it, PEG is attached to the dendrimers thereby slowing the process of break down. This fascinating particle offers significant promise for cancer treatment. They also offer other molecules to get attached on their surface easily. Researchers have found that dendrimers can be seen into a very sophisticated anti-cancer machines that carries five chemical tools – a molecule designed to bind with cancer cells, secondly, that fluorescence upon locating genetic mutations, followed by thirdly to assist in imaging tumor shape using x – rays, then fourth they are able for carrying drugs release on demand, and at last that would send a signal when cancerous cells are finally dead. So, finally scientists have found that dendrimers had successful tests with cancerous cells in culture and they decided to try them in living animal's cells soon.[30,31]

12. LIQUID CRYSTALS

The particles that possess both properties of solid and liquid are referred to as LIQUID CRYSTALS. They are made with different geometries and alternative polar and non-polar layers (i.e., a lamellar phase) that are form to pour aqueous drug solutions.[32]

13. HYDROGELS

A 3-dimensional, hydrophilic i. e, water loving, polymeric networks containing that means capable of imbibing large amounts of water or biological fluids are called HYDROGELS. They work for the regulation of drug release which is reservoir-based, controlled release systems or as carriers in swellable and swelling-controlled release devices.[33]

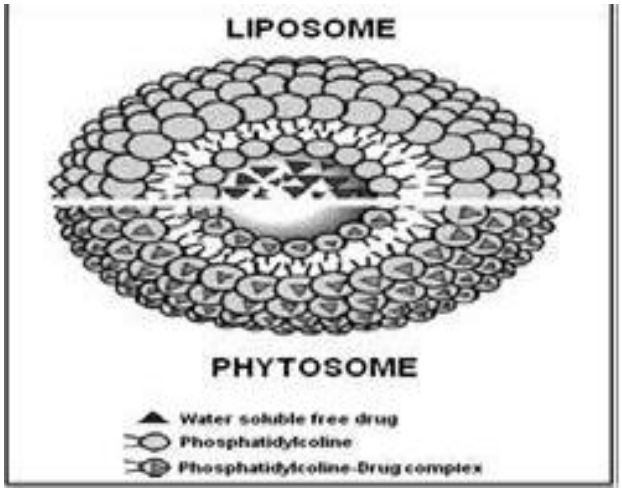

Figure 1: Structure of Liposome & Phytosome.

Upcoming Prospects and Opportunities In India For Future Generation

India is one of the countries with highest population so it also considered as the most strategic regions for the pharmaceutical market. Therefore, if we observe commercially many multinational entrepreneurs have been keen to invest and grow preferentially in this sector. Development is the key feature for the new and advanced techniques in the emerging field of NDDS which will create enormous demand for variety of excipients usage. India's diversity is well known for its quick adaptability to new excipients and associated technologies. So, if we consider commercially the excipients in India can grow on two criteria; first is the exportation of new organic excipients and the second is the employing of new excipients with various advanced delivery technologies. Majority of the pharmaceutical companies in the country have been applying the drugs to the patients with the help of Novel drug delivery systems. This eventually, in the upcoming era deals with enormous demand for the products and services offered by pharmaceutical and allied businesses. Nanotechnology provides different advanced applications in novel drug delivery systems that potentially enhance the diagnosis, treatment and help in monitoring of post-administration transformation of drug composition/ingredients within the body systems. Another major milestone that focused here is Computer Aided Drug Design, which offers a lot of scope for the development of such kind of novel and advanced systems. Computer Aided Drug Design provides designing and developing of drugs and delivery systems that consumes less time and resources and offers great accuracy and quality as compared to traditional methods.[34,35]

Molecular Imprinting Technology

The molecular imprinting technology emerges with great potential of satisfactory drug

dosage forms. This forms a pre-polymerization complex between the template molecule and functional monomers or functional oligomers (or polymers) with specific chemical structures that are designed for the interaction with the template either by covalent, non-covalent chemistry (self-assembly) or both. When pre-polymerization complex get formed, the polymerization reaction occurs in the presence of a cross-linking monomer with an appropriate solvent, which is able to control an overall polymer morphology and macro-porous structure. Meanwhile, once the template is removed, then the product formed will be of hetero-polymer matrix with specific identified elements for the template molecules.

Examples of MIP-based drug delivery systems include

(i) rate-programmed drug delivery, that provide drug diffusion from the system and has to follow a specific rate profile, (ii) activation-modulated drug delivery, where the release is activated by some physical, chemical or biochemical processes and (iii) feedback-regulated drug delivery, where the rate of drug release regulation is done by the concentration of triggering agent, such as a biochemical substance, whose concentration is dependent on the drug concentration in the body. Despite of having developed helpful applications of MIPs, the integration of the molecular imprinting approach for the development of DDS is just at its incipient stage. Nevertheless, it can be observed that, in the upcoming years, certain progress will proceed in this field, which would be advantageous for the improvements in the technology in different areas.

Evolutionary lines shows that such sort of contribution have several merits that are as follows; enhanced applicability of imprinting for drug delivery, increased applications of predictive tools for a rational design of imprinted systems and the development of molecular imprinting in water.[36]

Administration Routes

The choice of a delivery route should be done on focusing the maximum therapeutic effect which much has certain factors like patient acceptability, enhanced solubility, access to a disease location and effectiveness in dealing with the specific disease. The vital drug delivery route is the peroral route.

Recently, most of the increasing numbers of drugs are protein and peptide based. They provides the great compatibility for more highest therapeutics, but they are not able to cross mucosal surfaces and biological membranes easily; they are easily denatured or degraded,

prone to rapid clearance in the liver and other body tissues and require precise dosing. Presently, if we observe then we came to know across that protein drugs are usually administered by injection, but this route is less pleasant and also possesses more problems of oscillating blood drug concentrations. So, instead of having the barriers it is a successful drug delivery that exist in the gastrointestinal tract (i.e., acid-induced hydrolysis in the stomach, enzymatic degradation throughout the gastrointestinal tract by several proteolytic enzymes, bacterial fermentation in the colon), the peroral route is still the most precisely investigated as it provides advantages of convenience and cheapness of administration, and capability of being cost effective.

Pulmonary delivery is important too and is effected in different ways - through aerosols, metered dose inhaler systems (MDIs), powders (dry powder inhalers, DPIs) and solutions (nebulizers), all of which may contain nanostructures such as liposomes, micelles, nanoparticles and dendrimers. An aerosol product for pulmonary delivery contains more than 30% of the global drug delivery market. Researches show that lung delivery is driven by the potential for successful protein and peptide drug delivery, and by the promise offered of an effective delivery mechanism for gene therapy (for example, in the treatment of cystic fibrosis), as well as the requirement to replace chlorofluorocarbon propellants in MDIs. Pulmonary drug delivery provides local targeting for treating the respiratory diseases and emerges as to be a versatile choice for the delivery of drugs systemically. However, the pulmonary delivery of proteins suffers by proteases in the lung, that reduces the overall bioavailability and by the barrier between capillary blood and alveolar air (air-blood barrier) still it h advantages over them. To avoid the problems like gastrointestinal irritation, metabolism, variations in delivery rates and interference due to the presence of food researchers came with a solution named as TRANSDERMAL DRUG DELIVERY which is very much suitable for unconscious patients. This technique is generally developed with the conditions keeping in mind like non-invasive and aesthetically acceptable criteria, and can be used to offer local delivery over several days. Now if we talk about the limitations then it includes slow penetration rates, lack of dosage flexibility and / or precision, and a restriction to relatively low dosage drugs.[37]

CONCLUSION

Novel drug delivery system provides convenience in reducing the repeated administration to overcome noncompliance and also helps to increase the therapeutic value by reduced toxicity. It also possesses increased bioavailability, and so on. Further researches are also going on for

herbal drugs to integrate them with novel drug delivery systems. Enhanced bioavailability, reduced toxicity, sustained release action, protection from GI degradation led to establish advanced applications in novel drug delivery techniques for natural medicines which is not possible be obtain by conventional drug delivery system due to their large molecular size, poor solubility, degradation of herbal medicines in GI medium.

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