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RESEARCH ARTICLE

Herbal Nanotherapeutics: A noval approach for herbal drug delivery system

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ABSTRACT

Herbal treatment has been widely used around the globe since ancient times. The advancement of phytochemical and phytopharmacological sciences has enabled to characterize and identified of the composition and pharmacological activities of plant products. The effectivity of many of the variety of species of herbal medicinal plants are depends upon the presence of its active constituents. Many of the phytochemical component generally obtained by extracts, such as carbohydrate, flavonoids, glycosides, tannins, steroid and terpenoids. Some of the component are soluble in water but they have lower the rate of pharmacological activity, because they are unable to cross the biological cell membrane, which is lipidic in nature, thus the particles are poorly absorbed, resulting in lower the rate of bioavailability and efficacy in this way some of extracts are not used clinically because of these obstaclesand lower the rate of bioavailabiliy and higher the side effect. So now a days the herbal nanotechnology system has been widely proposed to overcome these type of problems, because nanostructured systems may have potential candidate for drug delivery and therapeutics system as well as decrease the side effect and loss of drug and increases the rate of transportation of drug through the biological membrane and this way it might be able to potentiate the action of plant extracts, reducing the required dose and side effects, and improving activity. Nanosystems can deliver the active constituent of herbals at a sufficient or minimum concentration during the entire treatment period, directing it to the desired site of action. Conventional treatments do not meet these requirements. The purpose of this study is to review a noval approach for delivery of herbal drug system via nanostructred herbal system.

INTRODUCTION

Knowledge and use of plants as herbal medicines has occurred in various people throughout human evolution, beginning when man was learning to take plants for food, and to relieve ailments and diseases (1). However, during the last few decades of the twentieth century, mainly in the Western world, now a day allopathic medicines are taken in place of herbal medicines. Allopathic therapy are now a day more widely used than traditional medicines, especially in western countries. However, many developing countries now a day's also use these natural medicines, most likely because getting a synthetic drug is expensive (2). According to the WHO, 80% of people in developing countries depend on alternative medicinal practices to meet and/or supplement their basic health needs (3).

Giving the chemical composition of herbal plants and their vast uses has become a research focus for all scientific society. This research may explore to more innovative products, with lesser side effects than existing drugs (4). There is a complex of structures of natural products, as well as their physicochemical and biological effects, has impressed researchers. However, in case of local health care needs, a less percentage of plants have been evaluated for their medicinal properties. That's why, there is a lack of information to describe any true potential (5, 6).

HERBAL APPROACHES OF NANOTECHNOLOGY

Unlike the allopathic system, the herbal treatment have number of constituents that all work together against the disailment. The natural substances produced by the organisms, e.g., animals, plants, fungi and bacteria act as biologically active agents. Nanotechnology is the new approach in the drug discovery, and it has the property of specific targeting in the sense that without the attachment of a specific ligand, these can be used for specific targeting, due to their very small size, at the infected pathological areas. Some of these formulations are already present in the market. The researchers have developed many types of novel formulations for development of herbal drugs. Phytochemical and phytopharmacological sciences have already established the combination and biological properties of several herbal plant products. Most of the therapeutically active constituents of extracts, such as tannins, flavonoids, and terpenoids, are highly water-soluble, but demonstrate a low absorption, because they are not able to cross lipid membranes, have higher molecular sizes, and show poor absorption, resulting in loss of bioavailability and efficacy. Some researches have demonstrated that herbal medicines have good action in assays in vitro, which are not repeated in experiments in vivo. Other than this, some important substances are rarely used, because they are incompatible with other

constituents in the formulation, or have undesirable effects (35).

NANOCARRIER DRUG DELIVERY SYSTEM FOR HERBAL MEDICINE

Polymeric Nanoparticles

Now a day, nanotechnological techniques involving medicinal plants have gained the focus of researchers, who have developed several innovative delivery systems, including polymeric nano particles. All these materials, produce from biodegradable and biocompatible polymers, represent an option for controlled drug delivery system. Nanoparticles made from Polymers are a stable formulation used for drug delivery, as they can be targeted (7, 8)

Nanoparticles made from polymers are colloidal systems that work as vectors to control drug release, and targeting it toward specific areas. obsereved against conventional formulations, Nanoparticles made from polymers can increase the solubility of constituents, improve absorption of the active components and reduce the therapeutic dose. Other than this, nanoparticles are advantageous when used in blood, because they are stable, nonthrombogenic, non-toxic, noninflammatory, nonimmunogenic, do not activate neutrophils, and avoid the reticuloendothelial scenario. Sometimes, Nanoparticles made from polymers are used to reach specific tissues, or work as a cell surface (9). Nanoparticles made from polymers can be synthesized using various methods, according to their intended application and payload. All these particles are made from artificial, natural, or biodegradable polymers. Herbal materials are preferred, because they generally have more importance, such as the ability to deliver more than one active constituent using the same carrier for system, increase residence time in the body, provide a sustained release system, and reduce side effects from it. (9).

Solid Lipid Nanoparticles

Solid lipid nanoparticles are colloidal carrier systems, developed in the early nineties, that combine the advantages of other colloidal systems (such as liposomes, emulsions and polymeric nanoparticles) for drug delivery, while minimizing, or avoiding, some of their drawbacks. 50 SLNs have higher physicochemical stability, and offer better protection from degradation of labile drugs; they also can be easily produced on a large scale (10, 11, 12).

Solid lipid nanoparticles are colloidal particles containing highly purified triglycerides, composed mainly of lipids that are solid at room temperature normally. All These structures are formed from solid lipids, or mixtures thereof, and stabilized by surfactants and colloids. Matrix of the lipid particle is solid; it can protect drug molecules against chemical deterioration. Sometimes, when the system is produced, crystallization occurs, resulting in low encapsulation efficiency and drug release from it (10). Pouring a liquid lipid (oil) to an oil/water

emulsion containing a solid lipid, or mixture of solid lipids, promotes the formation of Solid lipid nanoparticles (11). Because of their small size (50–1,000 nm) and biocompatibility, Solid lipid nanoparticles may be used in the pharmaceutical field for various routes of administration, such as percutaneous, oral and parenteral. (12).

Nanostructured Lipid Carriers

Nanostructured lipid carriers provide the efficiency of encapsulation and minimize the expulsion of active particles during encapsulation of drugs. Nanostructured lipid carriers are second-generation systems, and are seeking attention as alternative vehicles for colloidal drug delivery system. All These systems contain a mixture of lipid and solid phases that forms a unorganized liquid lipid matrix, which accommodates active substances in drug (10). Few examples of lipids used in the solid phase are glyceryl dilaurate, stearic acid, hydrine, cetyl alcohol and glyceryl monostearate,. And the examples of the liquid phase include oleic acid, caprylic/capric acid and glyceryl monodicaprylate,. There are many cases, approximately 5% of the drug (by weight) is used in the initial precursor mixture for Nanostructured lipid carriers, giving in drug loading efficiency of approximately 3% to 4%. Various routes may be used to give these formulations: intravenous, oral, dermal and pulmonary,. And the latter is advantageous, due to the films form occlusions, there is a controlled release profile, and the formulation is biodegradable and relatively nontoxic agents. Other than it, the small size of the two particles ensures contact with the stratum corneum, facilitating increased penetration of the drug into the skin of person (10).

Liquid Crystals

Liquid crystals are a two distinct phase of condensed structures that rest in a state intermediate between a crystalline solid and an isotropic liquid; they may be disordered or ordered, whereas indicated by their ease of efflux. The States of matter between solids and liquids are mesophases, which may be cubic or hexagonal in Liquid crystals. Liquid crystals are categorized according to two general provisions: lyotropic liquid crystals and thermotropic liquid crystals (13, 14). TLCs have temperature-dependent liquid-crystalline phases, and a specific temperature at which the liquid crystal becomes an isotropic liquid. The main constituent is the molecule that forms the mesophase. Lyotropic liquid crystals possess functional unit micelles, which are aggregates composed of amphiphilic molecules in it. Amphiphiles have a small polar (hydrophilic) part and a large (hydrophobic) apolar tailis there. The Mesophase formation is dependent on concentration, temperature and solvent, under certain conditions, micelles can self-organize, generating structures of great complexity is there (15). Liquid crystalline

mesophases are identified using measurements of their optical isotropy via, electron microscopy with cryofracture, neutron scattering at low angles,neutron diffraction, polarized light microscopy and X-ray scattering at low angle (13).

Liposomes

Liposomes are microscopic vesicles made of one or more concentric lipid bilayers, separated by an aqueous part. Hydrophilic substances are engaged in the aqueous compartment, while adsorbed lipophiles are inserted into the membrane layer. One by one, both types of substance can be encaged. All These vesicles consist primarily of phospholipids (synthetic or natural), sterols, and an antioxidant. The Liposomes are classified according to their size, surface charge and number of lamellae, As to surface charge, liposomes are classified as cationic, anionic, or neutral. With regards to form, size, and number of lamellae, liposomes can be classified as oligo, uni or multilamellar, and small, large, or big. Single lamellar liposomes (ULs) contain a single bilayer and are classified in various size ranges: small unilamellar liposomes (SUVs), with diameters of approximately 25–100 nm; large unilamellar liposomes, with diameters of 100 nm to 1 μm; and giant unilamellar lipo-some, with diameters greater than 1 μm, which reach sizes in the tens of microns (comparable to eukaryotic cell size). Many lamellar liposomes (MLVs) consist of many concentric lamellae, exhibiting an onion-like structure and shape. ULs are often found in dilute solutions of surfactants, whereas MLVs are found in more concentrated compartments (16, 17).

Microemulsion

The term (ME) can be define as a fluid system obtained by titration, composed of a simple emulsion along a medium chain alcohol, like pentanol or hexanol; initially semi-transparent, and titrated until clear (18). Microemulsion are transparent emulsions and in which an oil is dispersed in an aqueous medium (or vice-versa) containing a surfactant, with or without a suitable cosurfactant in it. These conditions produce a thermodynamically stable system, with droplets of the internal phase measuring on the nanounit. Substances which are active may be carried in the microemulsions when they are solubilized in the oil, or the aqueous phases of the emulsions (19). Microemulsion are reservoir systems, once the drug is separated from the dissolution medium through a membrane or interface that must be changed to control the release into the surrounding. All these systems provide a dimensionally restricted environment with private properties, and are capable of connecting or associating molecules of different groups of drugs, with the purpose of improving their solubility, bioavailability profile and modular stability (19-22).

Transfersomes

Transfersomes are prepared from phospholipids supplemented with single chain surfactant with a high radius of curvature which work as edge activators to provide vesicle elasticity and deformability to it (23). These Transfersomes are specific deformable vesicles, which are being developed, considering the advantage of phospho-lipids vesicles, for suitable drug delivery. Transfersomes are highly elastic in nature; as such they could easily overcome the skin penetration, by squeezing themselves in a self-adapting behavior and also they possess a unique ability to get accommodated with a wide range of solubility and work as an efficient carrier for both low as well as high molecular weight drugssuch as proteins, analgesic, hormones, anticancer drugs, corticosteroids, insulin, etc with high entrapment efficiency and a unique advantage of protection of the encapsulated drug, from being metabolically degraded. Transfersomes could be easily made using various methods such as modified handshaking process, suspension homogenization process, centrifugation process and aqueous lipid suspension process. Transfersomes shows potential advantages are highly utilized in Transdermal Immunization, Peripheral Drug Targeting & for Transdermal Delivery of Insulin, NSAIDs, Heparin, Anti Cancer drugs, etc. Capsaicin transferosomes are produced by the high shear dispersion technique and the penetration of capsaicin transferosomes was found to be more resulting better topical absorption as compared to pure active constituents (23, 24). Colchicines and Curcumin transferosomes were made by using hand shaking method, these formulation prevent drugs from gastro-intestinal side effect associated with oral administration and provide local, sustained and site specific delivery of colchicines and Curcumin (25). Transferosomes of vincristine were prepared by using lecithin and sodium deoxycholate in 70/20 ratio. This formulation increases the entrapment efficiency and improved skin penetration of the drug (26).

Ethosomes

Ethosome are very soft, malleable lipid vesicles composed mainly of phospholipids, alcohol (ethanol or isopropyl) in relatively high concentration (20-45%) and water in it (27). Ethosomes are novel lipid carriers and can be modified for enhanced skin delivery. Ethosome, as a novel liposome, is especially useful as a topical or trans-dermal administration carrier of the drug. It has a high deformability and entrapment efficiency and can penetrate through the skin layer (28). As compared to other liposome, the physical and chemical properties of ethosomes make the delivery of the drug through the stratum corneum into a deeper skin layer efficiently or even into the blood stream (29). This action is very important as the topical drug carrier and trans-dermal delivery system. Furthermore, the ethosomes carrier also provides an efficient intercellular delivery for both hydrophilic and lipophilic drug molecule.

Ethosome are medium for the delivery of large amount of diverse group of drug and this drug is administrated in semi solid form producing improved patient requirement (30). Ethosome suspension of ammonium glycyrrhizinate was prepared for the dermal administration of drug. The glycyrrhiznic ethosome increase in-vitro precutaneos permeation and significantly enhance its anti inflammatory activity of glycyrrhizin 39. Ethosome of *Tripterygium wilfordi* (Triptolide) were produced by controlling filming rehydration and ultrasonic method and evaluated in the rat model. This ethosomal formulation showed an increase in precutaneous permeability, high entrapment efficiency compared to their traditional formulation method (31). Ethosmoe of *Sesbania grandifolia* were prepared by solvent dispersion method that enhances the trans-dermal permeation of it. Like this ethosome of alkaloid of *Sephora alopecuroides* were developed by transmembrane pH active loading methods that enhance drug delivery and stabilityof the drug.

Microspheres

Microspheres are characteristically free flowing powders made of proteins or synthetic polymers which are biodegradable in nature and ideally having a less than 200 μm particle size (32). As a delivery system microspheres are beneficial because they can injected or ingested and: they can be trimmed for desired release profiles and used site-specific delivery of drug and in some cases can even provide release in specific organ-targeted. Microspheres of Curcuma longa oleoresin were prepared through emulsion solvent diffusion method and this formulation drud release very sustainably. Micro-encapsulation of Zeodary turmeric oil into microspheres via quasi-emulsion solvent diffusion has been used for bioavailability enhancement and sustained drug release of the drug. Oxidised cellulose microsphere containing *Camphtotecha acuminate* were devloped by using evaporation method, has been successfully use for very long release of camptothecin drug in it. Moreover microsphere of *sophora japonica* (Quercetin) has been devloped by solvent evaporation method that significantly decline the drug molecular size and this novel drug can easily pass through from blood barrier (33).

Herbosomes

Herbosome is a new approach in herbal drug technology that removes the limitations of the traditional drug delivery systems. Herbal medicines have been abundantly used all over the globe since ancient times and by physicians and patients for their better therapeutic value as they have no or less side effects as compared with modern medicines system like allopathic medicines. The Herbosome basically contain the active ingredients of the herb bounded to phospholipids for targeting. The molecular structure of phospholipid contains a water-soluble head and two fat-soluble tails due to this dual solubility, the phospholipid acts as an

effective emulsifier for drug. By mixing the emulsifying action of the phospholipids with the standardized botanical extracts, the herbosome form provides potentially enhanced bioavailability for lipid soluble drugs explained by faster and improved absorption in the intestinal tract of a person. Herbosome technology has been effectively used to increase the bioavailability of many popular herbal extracts and phytoconstituents including Ginkgo biloba, green tea, grape seed, hawthorn, milk thistle and ginseng can be produced for various therapeutic uses and diet supplements. This method can increase the rate and the extent of drug absorption across the lipoid bio-membrane, which has been showing effectand appropriate delivery system.

Nanocrystals

The microscopic crystals of a pharmaceutical product can make it soluble in water even if the bulk compound is not there. These tiny size particles means a much greater surface area to volume ratio giving access to more water molecules that can surround the particles, which is the important for dissolving any drug. This action can then allow the particles to be carried across the lining of the gut wall where they would previously simply move fast with no interaction with other things. A demonstration of gymnemic acids derived from the herb Gymnema sylvestre, can be prepared more readily bioavailable by making the active compounds as nanoscopic crystals, known as Nanocrystals (34). These substances show medicinal activity in a range of diseases, in particular diabetes mellitus, with the native herb having been used in traditional medicine for several decades. The Nanocrystals of gymnemic acids could provide important clues as to how to transfer the medical benefits of the herb to a regulated pharmaceutical product for further more scientific investigation and with a more specific study of diseases.

CURRENT APPROACH IN HERBAL NANOTECHNOLOGY:-

Nano sized drug delivery systems for herbal drugs can potentially enhance the biological activity and overcome problems associated with medicines produced from plants. Other than this, significant challenges remain for implementation of clinically viable therapies in this platform. Trials of novel methods to control the interactions of nanomaterials with biological systems show some of the current challenges to transfering these technologies to therapies. There are new challenges in the development of nanotechnology-based drug delivery systems which is the feasibility of scale-up processes that bring innovative therapeutic techniques to the market quickly, and the possibility of obtaining multifunctional systems to fulfill several biological and therapeutic requirements for the drugs. Furthermore additional new challenges include probing the targeting efficiency of nanoparticles, and satisfying international standards for their toxicology and biocompatibility.

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