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### Nano Carriers of Novel Drug Delivery System for “Ayurveda Herbal Remedies” Need of Hour– A Bird’s Eye View

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#### ABSTRACT

Ayurveda pharmacopeia is based upon herbal, mineral and herbo-mineral natural products but herbs takes first rank in pharmaceutics. Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. Unlike the existing allopathic system, the herbal remedies have hundreds and thousands of constituents that all work together against the diseases. Mostly, the conventional pharmaceuticals or pharmacognostical products in the market are rooted from natural products and their derivatives with herbal products playing pivotal role. All over the world, the research on these herbal remedies has been carried out in the different fields’ for instance pharmaceutical chemistry, pharmacognosy, pharmacology and clinical therapeutics. ‘Nanotechnology’ is the new emerging technology in the drug discovery and it has the property of self targeting in the sense that without the attachment of a specific legend, these can be used for targeting, due to their distinctively small size, at the infected pathological areas. Some of such formulations are already present in the market and many more are expected to come by 2020 after their success in ongoing clinical trials. Drug delivery research is clearly moving from the micro- to the nanosize scale. Nanotechnology is therefore emerging as a field in medicine that is expected to elicit significant therapeutic benefit. Nanoparticles are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. A nanocarrier is nanomaterial being used as a transport module for another substance, such as a drug. Nanocarriers are currently used in drug delivery and their unique characteristics demonstrate potential use in chemotherapy. Herbal remedies may be selected as feasible drug candidate for delivery through a nano delivery system. It is being assumed that the “herbal remedy” with the nanocarriers will increase its potential for the treatment of various chronic diseases and health benefits. In this review, author has made an effort to explore this new approach is escalating the interest of number of scientists to improve and to accelerate the joint drug discovery and development of novel nano delivery systems for ayurveda herbal remedies.

**Keywords:** Natural products, Herbal remedies, Nanotechnology, Nanoparticles, Novel Drug Delivery System,

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## INTRODUCTION

Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines.<sup>1</sup> Phytotherapy is the study of the use of extracts of natural origin as medicines or health-promoting agents. Phytotherapy medicines differ from plant-derived medicines in standard pharmacology. Where standard pharmacology isolates an active compound from a given plant, phytotherapy aims to preserve the complexity of substances from a given plant with relatively less processing. Modern phytotherapy, following the scientific method, can be considered the study on the effects and clinical use of herbal medicines.<sup>2</sup> On other hand, the Ayurveda pharmacopeia is based upon herbs, mineral and herbo-mineral natural products but herbs are ranking in first order. Ayurveda advocates using drug as “wholesome” without isolating its natural chemical components. Phytotherapeutics need a scientific approach to deliver the components in a sustained manner to increase patient compliance and avoid repeated administration. This can be achieved by designing novel drug delivery systems (NDDSs) for herbal constituents. NDDSs not only reduce the repeated administration to overcome non-compliance, but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability, and so on<sup>3</sup> (a,b)

Nanotechnology is a field of applied science and technology which aims to develop devices and dosage forms in the range of 1 to 100 nm. The applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems have recently been referred to as nanomedicine. The nanocarriers have been made of safe materials, including synthetic biodegradable polymers, lipids, and polysaccharides<sup>4</sup>

### **Activity of herbal medicines:**

The activity of herbal medicines depends on overall function of a variety of active components, as all the constituents provide synergistic action and thus enhance the therapeutic value. Each active constituent plays an important role and they are all related to each other. However, most of the herbal origin drugs possess insoluble character leading to lower bioavailability and increased systemic clearance requiring repeated administration or higher dose, which makes the drug as a poor candidate for therapeutic use.

In phyto-formulation research, developing nano dosage forms (Polymeric Nanoparticles (Nanospheres and Nanocapsules), Liposomes, Proliposomes, Solid Lipid Nanoparticles (SLNs), (Nanoemulsion) etc. has large number of advantages for herbal drugs, including enhancement of

solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation, etc. Thus, the nano-sized drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines. Hence, integration of the nanocarriers as a NDDS in the traditional medicine system is essential to conflict more chronic diseases like asthma, diabetes, cancer, Rheumatism, Parkinson's and others<sup>5</sup>

### **History and Development of Nanotechnology in Drug Delivery System:**

Since ancient days, natural products, including plants, have been the basis of treatment of human diseases. The basis of concept of modern medicine development remains rooted in traditional medicine and therapies<sup>6</sup> (a,b) In different parts of the world like ancient China, Egypt, Africa, America, and India, plants had been used for medicinal purposes long before recorded history. Chemical analysis first became available in the early 19th century which started the extraction and modification of herbal ingredients<sup>7</sup>.

The concepts that seeded nanotechnology were first discussed in 1959 by renowned physicist Richard Feynman in his talk There's Plenty of Room at the Bottom, in which he described the possibility of synthesis via direct manipulation of atoms. The term "nano-technology" was first used by Norio Taniguchi in 1974, though it was not widely known<sup>8</sup>. In the realm of medicine, nanotechnology holds enormous promise for benefit of the society by potentially reducing the miseries of people suffering from grave illnesses and save a great number of lives. Traditional Oriental medicine (such like Ayurveda) would greatly benefit by integrating with the scientific advancements in medical science and diagnostics in concert with nanotechnology. This trinity may usher in a new era of affordable, safe and effective medicinal system.

### **Categories of controlled-release drug delivery system:**

There are three main categories of controlled-release drug delivery system namely Intravenous, Transdermal, and Oral systems. Oral osmotically controlled release (CR) delivery system provide a uniform concentration/amount of drug at the site of absorption and thus after absorption, allow maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces the frequency of administration.

### **Ayurveda and Oral Drug-delivery System:**

Oral route of administration is one of the oldest and most widely used routes for the administration of drug providing convenient method of efficiently achieving both local and systemic effect. In conventional drug delivery systems, there is little or no control over release of

the drug and effective concentration at the target site can be achieved by irregular administration of grossly excessive doses. This kind of dosing pattern result is frequently changing, erratic and sub or supra therapeutic plasma concentrations, leading to marked side effects in some cases<sup>9</sup> Ayurveda refers that if drug is being induced internally in human body then it should be passed through metabolism (*Agni-Vyapar*). Hence, oral drug delivery system is advocated for most of drugs.<sup>10</sup>

#### **Nanotechnology in Drug Delivery System:**

For over 20 years, researchers have appreciated the potential benefits of nanotechnology in providing vast improvements in drug delivery and drug targeting. Improving delivery techniques that minimize toxicity and improve efficacy offers great potential benefits to patients, and opens up new markets for pharmaceutical and drug delivery companies. Other approaches to drug delivery are focused on crossing particular physical barriers, such as the blood brain barrier, in order to better target the drug and improve its effectiveness; or on finding alternative and acceptable routes for the delivery of protein drugs other than via the gastro-intestinal tract, where degradation can occur.

#### **Role of Administration of Ayurvedic herbs:**

The biggest challenge to drug delivery into the CNS is bypassing the blood-brain barrier (BBB) as it limits access to the CNS. For decades, the BBB has prevented the use of many therapeutic agents for treating brain-related diseases and injuries, including Alzheimer Disease , stroke, brain tumor, head injury, and other CNS disorders. Ayurveda relies on some novel methods of administering herbs or their preparations (or both) to treat CNS disorders. However, proper studies are lacking to demonstrate whether these herbs or their components given orally or by some other means cross the BBB and reach the CNS. One novel method of herbal delivery, called 'NASYA', involves intranasal delivery of dry herbal powders or medicated oils and is a practical, non-invasive, rapid, and simple method to deliver the therapeutic agents into the CNS. The use of medicated oils, which require that the herbs be cooked in four parts oil and 16 parts water over a low flame until all of the water evaporates, ensures the transport of lipophilic and lipid-soluble molecules across the BBB membrane, where hydrophilic compounds demonstrate minimal permeation. Intranasal administration offers numerous benefits for drug delivery into the CNS, and interest in this non-invasive route of administration has increased. The delivery is rapid, bypasses the BBB, and directly targets the CNS, thereby reducing systemic exposure and side effects.

#### **Tremendous advancements in drug delivery:**

Tremendous advancements in drug delivery, oral administration of therapeutic agents still remains the favored route for majority of clinical applications, due to the excellent accessibility, and patient compliance as well as the preferred alternative route of drug administration for non-invasive drug delivery among the other various routes is Novel drug delivery system. The correlation between drug intake and a clinical response is complex enough, the choice and design of the ideal pharmaceutical dosage form of a drug delivery system would be critically important to reach a progress in superior drug development. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development<sup>11</sup>.

#### **Uncontrolled rapid release of drug and systemic toxicity:**

The rate and extent of absorption of drug from conventional formulations may vary greatly depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Uncontrolled rapid release of drug may also cause local gastro intestinal or systemic toxicity. Hence better dosage form design and delivery can minimize many of these problems. Various approaches are made in designing the formulations, which will overcome the disadvantages of conventional dosage forms, which include sustained/controlled drug delivery system.

#### **Novel Drug Delivery System:**

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceuticals, bio-conjugate chemistry, and molecular biology. Among drug carriers one can name soluble polymers, micro-particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with

specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting:

- An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

### **Controlled drug release and subsequent biodegradation are important for developing successful formulations.**

Potential release mechanisms involve:

- (i) Desorption of surface-bound /adsorbed drugs
- (ii) Diffusion through the carrier matrix
- (iii) Diffusion (in the case of nanocapsules) through the carrier wall
- (iv) Carrier matrix erosion
- (v) A combined erosion /diffusion process.

The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature).

### **Nano- Particles:**

Nano-particles (including nanospheres and nanocapsules of size 10-200 nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers can be formed from both biodegradable polymers and non-biodegradable polymers. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the

controlled release of drugs, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the per oral route.

### **Nano Carriers**

A nanocarrier is nanomaterial being used as a transport module for another substance, such as a drug. Commonly used nanocarriers include micelles, polymers, carbon-based materials, liposomes and other substances<sup>12</sup>. Nanocarriers are currently used in drug delivery and their unique characteristics demonstrate potential use in chemotherapy. Nanocarriers include polymer conjugates, polymeric nanoparticles, lipid-based carriers, dendrimers, carbon nanotubes, and gold nanoparticles. Lipid-based carriers include both liposomes and micelles. Examples of gold nanoparticles are gold nanoshells and nanocages<sup>13</sup>.

Different types of nanomaterial being used in nanocarriers allows for hydrophobic and hydrophilic drugs to be delivered throughout the body. Since the human body contains mostly water, the ability to deliver hydrophobic drugs effectively in humans is a major therapeutic benefit of nanocarriers<sup>14</sup>. Micelles are able to contain either hydrophilic or hydrophobic drugs depending on the orientation of the phospholipids molecules. Some nanocarriers contain nanotube arrays allowing them to contain both hydrophobic and hydrophilic drugs. New research is being conducted to invent more effective, safer nanocarriers. Protein based nanocarriers show promise for use therapeutically since they occur naturally, and generally demonstrate less cytotoxicity than synthetic molecules<sup>15</sup>.

### **Herbal remedies and Nano delivery system:**

Herbal remedies may be selected as feasible drug candidate for delivery through a nano delivery system because of the following properties:

1. Effective chloroform, petrol, acetone, and methanolic extracts are available which may not be suitable for delivery as such.
2. These are the bulk drugs so dose reduction is intended.
3. Currently marketed formulations lack target specificity for various chronic diseases.
4. Some other side effects are associated with currently marketed formulations.
5. Patient non-compliance due to large doses and less effectiveness with the available formulations.

### **Future Prospective:**

All over the world, the research has been going on herbal remedies and natural products. The development of herbal remedies in the drug delivery system in a number of institutes is being carried out at basic and clinical trial levels. The only requirement is to develop the better systems

for the proper delivery of such drugs at the sites and in the whole body in the doses which will not compromise with the existing treatment. Something, that would not only give relieve from side effects like toxicity and hypersensitive reactions but also will increase the patient's strength from inside is very much desirable. The first motto of Ayurveda reflects that “Prevent first to natural health as acquired at time of birth which contains the natural (by born) immunity, that increases the strength from inside is very much what ever and wherever desirable.

In the future, the concept of herbal nanoparticles for drug delivery as a “nano” may also fascinate some potential research groups and potentially create attention-grabbing results. Hence, using “Ayurveda herbal remedy” in the nanocarriers will increase its potential for the treatment of various chronic diseases and health benefits. Many successful examples with experienced evidences are present among us in the direction of nano research. Herbal remedies are also prosperous resources of advantageous compounds holding antioxidants and constituents that can be made use in purposeful foods<sup>16</sup>.

This type of collaborative research among the Aurveda “Herbal remedies” and newer approaches of modern drug delivery system, i.e., “Nanotechnology” has established the attractive therapies to the pharmaceutical in near future that will enhance health of people. It is anticipated that the effectual and valuable relevance of the natural products and herbal remedies being applied with the nanocarrier will enhance the significance of existing drug delivery systems.

#### CONCLUSION:

Hence, using “Ayurveda herbal remedy” in the nanocarriers will increase its potential for the treatment of various chronic diseases and health benefits. Many successful examples were observed with the direction of nano research. Herbal remedies are also prosperous resources of advantageous compounds holding antioxidants and constituents that can be made use in purposeful foods. This type of research among the Ayurveda “Herbal remedies” and newer approaches of modern drug delivery system, i.e., “Nanotechnology” has the attractive therapies to the pharmaceutical in near future that will enhance health of people. It is anticipated that the effectual and valuable relevance of the natural products and herbal remedies being applied with the nanocarrier will enhance the significance of existing drug delivery systems.

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