



AN OVERVIEW OF NOVEL FORMULATION METHODS OF HERBAL SILVER NANOPARTICLES

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ABSTRACT

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The primary goals for research of nanotechnology in drug delivery include more specific drug targeting and delivery, reduction in toxicity while maintain therapeutic effects, greater safety and biocompatibility and faster development of new safe medicines. In recent years, nanotechnology-based formulations have given new lease of life to such problems with their myriad of formulations that include nanospheres, nanocapsules, liposomes, proliposomes, solid lipid nanoparticles [SLNs] and nano-emulsion. Combining herbal drugs with nanotechnology may potentiate the action of the plant extracts or active constituent by increasing their solubility, bioavailability and efficacy as well as by reducing the required dose and side effects. Silver nanoparticles (AgNPs) are increasingly used due to their unique physical and chemical properties in various fields such as medical, food, health care, consumer, and industrial purposes. These include optical, electrical, and thermal, high electrical conductivity and biological properties. Due to their peculiar properties, they have been used for several applications. Therefore, the objective behind presenting this review is to outline works on the formulation methods of herbal silver nanoparticle formulations.

INTRODUCTION

Nanotechnology

The objective of any drug delivery system is to deliver a therapeutic amount of drug to the site of action and to maintain the desired amount of drug level in the tissue or the body that can elicit a desired pharmacological effect without causing any serious adverse reactions¹. Nanotechnology is one of the fastest developing sciences over the last few years. This is an inter-disciplinary science that connects knowledge of biology, chemistry, physics, engineering and material science.² Nano word comes from the Greek word “nanos” meaning “dwarf”. Nano typically is defined as one billionth of a quantity or term that represents mathematically as 1×10^{-9} or simply as 10^{-9} . It is the science of very



small, virtually any science that involves understanding the world at the atomic level, manipulating material on the scale of atoms and molecules.³ Nanoparticles are small solid colloidal particles which are available in range from 10 to 1000 nm (1.0 μm), in which the active drug or biologically active material are dissolved, entrapped, and/or to which the active principle is adsorbed or attached. Goal of nanotechnology is same as that of medicine, to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach⁴. Drug delivery and related pharmaceutical development in the context of nanomedicine should be viewed as science and technology of nanometer scale complex systems, consisting of at least two components, one of which is a pharmaceutically active ingredient.

Metallic Nanoparticles^{5,6}

Metallic nanoparticles have fascinated scientist for over a century and are now heavily utilized in biomedical sciences and engineering. They are a focus of interest because of their huge potential in nanotechnology. Metal nanoparticles exhibit a rich optical phenomenology due to the excitation of Plasmon resonances. Today these materials can be synthesized and modified with various chemical functional groups which allow them to be conjugated with antibodies, ligands and drugs of interest and thus opening a wide range of potential applications in biotechnology, magnetic separation and preconcentration of target analytes, targeted drug delivery, vehicles for gene and drug delivery and more importantly diagnostic imaging. Silver nanoparticles (AgNPs) have emerged as an arch product from the field of nanotechnology. Silver has gained interest over the years because of distinctive properties, such as good conductivity, chemical stability, catalytic and antibacterial activity.

Silver Nanoparticles⁷

Silver is a soft white lustrous element. Metallic silver itself is insoluble in water, but metallic salts such as AgNO_3 and silver chloride are soluble in water. AgNPs are unique in nanoscale system due to the ease in its synthesis and chemical modifications. AgNPs are used in the development of new technologies in the areas of electronics, material sciences and medicine and because of their extensive applications in various areas more research is being conducted on the AgNPs by the scientists throughout the world.

History⁸

For thousands of years silver has been used as a healing agent by civilizations throughout the world. Its medical, preservative and restorative powers can be traced as far back as the ancient Greek and Roman Empires. Long before the development of modern pharmaceuticals, silver was employed as a "germicide". The Greek used silver vessels to keep water and other liquids fresh. The writings of Herodotus, the Greek Philosopher and historian, date the use of silver to before the birth of Christ. The Roman Empire stored wine in silver urns to prevent spoilage. In Middle Ages, silverware protected the



wealthy from full brunt of the plague. In the Early 1900s, people would put silver coins in milk bottles to prolong the milk's freshness. Hippocrates, the "father of medicine", wrote that silver had beneficial healing and anti-disease properties, in 1800's, doctors used silver sutures in surgical wounds with very successful results.

In the early 1900s, silver gained regulatory approval as an antimicrobial agent. Prior to the introduction of antibiotics, colloidal silver was used as a germicide and disinfectant. Physicians used it as an eye drop for ophthalmic problems, for various infections, and sometimes internally for diseases such as tropical spruce, epilepsy, gonorrhea, and the common cold. Colloidal silver preparations (CSP) were used to treat or prevent gonorrhea and gonorrheal conjunctivitis. In Ayurvedic medicine, silver is used in small amounts as a tonic, elixir or rejuvenate agent for patients debilitated by age or diseases. Medicinal silver compounds were then developed and silver became commonly used as a medicine. By early part of 1900's use of silver was becoming widespread. By 1940 there were approximately four dozen different silver compounds on the market. A new silver-based bandage has recently been approved by the FDA and licensed for sale. Nanosilver may have different shapes, such as spheres, rods, cubes etc., at nano scale, the silver particles exhibit deviating physico-chemical properties and biological activities compared with the regular metal. This is due to the higher surface area per mass, allowing a large number of atoms to interact with their surroundings. Due to the properties of silver at the nanoscale, nano-silver is now a days in an increasing number of consumer and medicinal products. The widest and best-known use of silver in medicine is in combination with sulfadiazine, where it becomes a topical antibacterial agent for the treatment of burns.

Properties of Nanosilver

Nanosilver has biological properties which are significant for consumer products, food technology, textiles and medical applications (e.g., Wound care products, implantable medical devices). In addition, nanosilver has unique optical and physical properties that are not present in bulk silver, which are claimed to have great potential for medical applications. Nanosilver have multifunctional properties such as antibacterial, Antifungal, Anti-inflammatory, Antiviral, Cancer therapy, Diffusion through glycoprotein film, Prevention of bio film formation, Surface Plasmon resonance.

Impact Of Nanosilver on Biomedicine

The recent emergence of nanotechnology has provided a new therapeutic modality in silver nanoparticles for use in medicine. Silver powder was believed by Hippocrates, father of modern medicine, to have beneficial healing and anti-disease properties and listed as a treatment for ulcers. Silver compounds were major weapons against wound infection in World War I until the advent of antibiotics upon reaching nanoscale, like other nano- materials and



primarily by virtue of extremely small size, silver particles exhibit remarkably unusual physicochemical properties and biological activities. These distinctive properties extend its application in antibacterial, antifungal, anti-viral and anti-inflammatory therapy.

Applications of Nanosilver

Due to the multifunctional properties of Nanosilver, it is widely used in all fields such as electronics, food products, personal care & cosmetics, household products, medicinal products etc., The application of nanosilver in the consumer products is mainly based on the antibacterial property of silver. Currently the application of nanosilver in medical products is emerging in the field of medical devices and pharmaceutical research and development.

Herbal Medicine

History of Traditional Herbal Medicine

Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous systems of medicine. Traditional preparation comprises medicinal plants, minerals and organic matters etc. Herbal drug constitutes only those traditional medicine that primarily use medicinal plant preparations for therapy. The ancient record is evidencing their use by Indian, Chinese, Egyptian, Greek, Roman and Syrian dates back to about 5000 years. About 500 plants with medicinal use are mentioned in ancient texts and around 800 plants have been used in indigenous systems of medicine. In India around 20,000 medicinal plant species have been recorded recently⁹, but more than 500 traditional communities use about 800 plant species for curing different diseases¹⁰. Currently 80 % of the world population depends on plant-derived medicine for the first line of primary health care for human alleviation because it has no side effects. Plants are important sources of medicines and presently about 25% of pharmaceutical prescriptions in the United States contain at least one plant-derived ingredient. In the last century, roughly 121 pharmaceutical products were formulated based on the traditional knowledge obtained from various sources. Indian subcontinent is a vast repository of medicinal plants that are used in traditional medical treatments, which also forms a rich source of knowledge. The various indigenous systems such as Siddha, Ayurveda, Unani and Allopathy use several plant species to treat different ailments¹¹.

Medicinal plants play an important role in the development of potent therapeutic agents. Herbal medicines are currently in demand and their popularity is increasing day by day. World Health Organization (WHO) has distinct herbal drugs as complete, labeled medicinal products that have vigorous ingredients, aerial or secretive parts of the plant or other plant material or combinations. World Health Organization has set precise guidelines for the evaluation of the safety, efficacy, and quality of herbal medicines¹². Herbal drug is a chief constituent in traditional medicine and a common constituent in Ayurvedic, Homeopathic, Naturopathic and other medicine systems. Herbs are usually considered as safe since they belong to natural sources²⁰. The use of herbal drugs due to toxicity and



side effects of allopathic medicines, has led to rapid increase in the number of herbal drug manufacturers. For the past few decades, herbal drugs have been more and more consumed by the people without prescription. Some drugs have been discontinued due to their toxicity, while others have been modified or combined with additional herbs to counterbalance side effects¹³.

Modern Medicine from Higher Plants

Medicinal plants play a vital role for the development of new drugs. During 1950- 1970 approximately 100 plants based new drugs were introduced in the USA drug market including Deserpidine, Vinblastine and Vincristine which are derived from higher plants. From 1971 to 1990 the new drugs such as Etoposide, Teniposide, Nabilone, Plaunotol, Lectinan, Artemisinin and Ginkgolides appeared all over the world 2% of drugs were introduced from 1991 to 1995 including Paciltaxel, Toptecan, Irinotecan etc. Plant based drugs provide outstanding contribution to modern therapeutics; for example: serpentine isolated from the root of Indian plant *Rauwolfia Serpentina* in 1953, was a revolutionary event in the treatment of hypertension and lowering of blood pressure. Vinblastine isolated from the *Catharanthus Roseus*. It is used for the treatment of Hodgkin's choriocarcinoma, non- Hodgkin's lymphomas, leukemia in children, testicular and neck cancer²². The mechanism of action of the plant derived micro molecules induced venom neutralization need further attention, for the development of plant-derived therapeutic antagonist against snakebite for the community in need. The above drugs came into use through the screening study of medicinal plants because they showed fewer side effects, were cost effective and possessed better compatibility.

Role of World health organization (WHO) in Phyto Medicine

In 1991 WHO developed guidelines for the assessment of herbal medicine, and the 6th International Conference of Drug Regulatory Authorities held at Ottawa in the same year ratified the same. The salient features of WHO guidelines are: **1) Quality Assessment:** Crude plant materials or extract plant preparation and finished product. **2) Stability:** Shelf life. **3) Safety Assessment:** Documentation of safety based on experience and toxicological studies. **4) Assessment Of Efficacy:** Documented evidence of traditional use and activity determination (Animals and human).

Methods Of Herbal Nanoparticles

High Pressure Homogenization Method

High-pressure homogenization (HPH) has been employed for unit operations like comminution, mixing, and stabilization of pharmaceutical solids and nanoparticles. The present chapter give useful insights on the fundamentals associated with in the process of HPH of colloidal dispersions, basic instrumentation of homogenizers, and theories on forces involved in homogenization. With advancing nanotechnology, the HPH technique has go through discernible evolution and has widen the scope of its pharmaceutical applications by facilitating particle engineering.¹⁴ An in-depth understanding of



fluid dynamics has helped the researchers confine innovative designs for high-pressure homogenizers with higher processing capacity and efficiency. HPH has the distinct advantage of being one of the most flexible and ductile processing methods for the preparation of distinct vesicular as well as non-vesicular lipid-based nano systems such as nano emulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanocrystals, as well as polymeric nanoparticles.¹⁵ The chapter has summarized the effect of various processing as well as product variables on features of the previously mentioned nanoparticle formulations. The chapter gives an extensive overview of the processing attributes of HPH that may facilitate the development of nanoparticles to attain advantageous pharmaceutical attributes.¹⁶

Solvent Emulsification-Diffusion Method

Nowadays, several methods for producing submicron particles from polymers are available. The emulsification diffusion (E-D) method was proposed as a substitute to avoid the toxicity-solvent problems caused by the emulsification-evaporation; additionally, its simple implementation, high reproducibility and flexibility have been committed for different research groups.¹⁷ This method is one of the first techniques analyzed from a mechanistic point of view as well as it has been used to encapsulate several types of drugs, including peptides and proteins. The purpose of this chapter is focused on the study of the pharmaceutical impact of the emulsification-diffusion method since it was introduced. We review and describe the critical preparative variables, constitutive materials, formation mechanisms as well as performance of the E-D method. The second part of the chapter contains an extensive collection of different types of drug-loaded nanoparticles derived by this method. Finally, some novel innovations as well as uses of the method have also been compiled.¹⁸

Salting-Out Method

A simple proposal for composition of protein-based nanoparticles is the salting out of a protein solution to form protein coacervates. shows the schematic diagram of the salting out method for preparing SF nanoparticles. Briefly, the silk fibroin solution was mixed with potassium phosphate. Proteins have hydrophilic and hydrophobic parts. Hydrophobic parts can comprise with the water molecules and allow proteins to form hydrogen bonds with the surrounding water molecules.¹⁹ With the enhance of the salt concentration, the salt ions attract some of the water molecules, resulting in the removal of the water barrier between protein molecules and the enhance of the protein-protein interactions. Therefore, the protein molecules combine together by forming hydrophobic interactions with each other and precipitate from the solution. Lammel et al. reported the formation of SF nanoparticles with an average diameter of 486~1200 nm in an all-aqueous process by salting out with potassium phosphate (>0.75 m).²⁰ The resulting particles were then kept in the refrigerator for 2 h and could be accumulate by centrifugation. When using 1.25 m potassium phosphate (pH 8), enhancing the concentration of SF can result in larger particles. Below pH 5 the particles combined into no dispersible clusters. The small molecule model drugs, such as alcian blue, rhodamine B, and crystal violet, were packed into the SF



particles by simple absorption based on electrostatic interactions. The drug-loaded SF nan particles showed a controlled release property, which depends on charge–charge interactions between the compounds and the SF.²¹

Nanotoxicology Of Silver Nanoparticles

Colloidal Nanosilver has been administered as a medication for almost one hundred years. One early example is a study from 1924 in which the behavior of collar Gol Nanosilver in the human body is described. Numerous cases of the nontoxic, cosmetic condition argyria were documented during this period (argyria is a condition characterized by bluish grey discoloration of skin). The toxicity of silver is considered to be relatively low & toxic effects on human other than argyria are only observed at very high concentrations. (e.g., Acute oral LD50 for rats is higher than 1600mg/kg/d). Contrary to many assumptions Nanosilver materials have a deep historical record of demonstrated safe use together with a long period of formal & successful regulatory oversight. Historical perspective also shows that Nanosilver has been intentionally manufactured & adopted commercially across a wide spectrum of every day applications for decade. For example, EPA registered silver nanoparticles have been safely used in down the drain & high-volume water contact applications (e.g., Swimming pool algicides & drinking water filter system) bringing benefit to millions of consumers over a period of 50 years. The US FDA has established a safety guideline for daily oral intake of silver, called Reference Dose or RID which is EPA's suggested limit for total daily intake of silver from all sources, including drinking water & Food. Silver Safety committee announced that 5µg/kg/day is safe limit of use of silver products from any source.

Need for NDDS "Nano Carriers" For "Herbal Remedies"

The activity of herbal drugs is depending on overall function of active components, as all the constituents provide synergistic active moiety plays a vital role and they are all related to each other³⁸. However, most of the herbal origin drugs possess low lipid solubility character leading to lower bioavailability and increased systemic clearance requiring frequent administration or higher dose, which makes the drug as a poor candidate for therapeutic use. The discovery of nanotechnology is considered as a milestone in medicine world. In case of herbals, nanotechnology becomes a great remedy to overcome the problems arising nowadays. In herbal formulation research, developing nano dosage forms has large number of advantages for herbal drugs, including increase: in the solubility and bioavailability, prevention from toxicity, greater biological activity, enhancement of stability, improving tissue macrophages distribution, controlled delivery, protection from physical and chemical degradation, and changes²².

Commercialization of Herbal

Commercialization efforts in herbal medicine by nanotechnology have now started around the world. Of the 300 companies identified actively involved in nano formulation worldwide, 259 are start-ups



and small and medium-sized enterprises focus on the development of nanotechnology-enhanced Phyto pharmaceuticals and medical equipment's and devices. Further, 41 another major pharmaceutical and medical device corporation have nanomedicine products on the market or run development projects in which nanotechnology plays a vital role. Over the past decade, 38 nanotechnology-enhanced medical products were placed on the market with estimated total sales of EUR 5.4 billion in 2004²³.

Strategies of Nanotechnology as NDDS

Drug delivery system fetched NDDS for a novel approach to overcome the drawbacks of the traditional drug delivery systems⁴¹. Nano-sized delivery system was selected because they appear to deliver high concentrations of drugs to disease sites because of their unique size and high loading capacities also, the deliver the drug in the small particle size that enhances the entire surface area of the drugs allocating quicker dissolution in the blood²⁴. The NDDS shows enhanced permeation and retention effect, i.e., enhanced permeation through the barriers because of the small size and retention due to poor lymphatic drainage such in tumor. In another aspect of selection of NDDS they exhibit passive targeting to the disease site of action without the addition of any particular ligand moiety. In addition, may reduce the frequency, dose, and the side effect²⁵.

Recent Development

The nanoparticles now have been coming as the capable approach in drug delivery systems for the well-organized delivery of herbal drugs utilized in the treatment of many critical diseases such as cancer by crossing the reticulo-endothelial system, increased permeability and retention effect, and tumor-specific targeting²⁶.

Recently, pharmaceutical researcher has shifted their focus to designing a drug delivery system for herbal medicines using a modern approach. The oral absorption of drug is limited its chemical constituents such as flavonoid and lignin. In the recent years, nanostructured carrier systems such as micro-emulsion, polymeric nanoparticles, liposomes, sliver nano materials, SLNS, polymeric micelles, nano-emulsions, micro sphere have been discovered for their potential to deliver anticancer drugs by oral route²⁷. Moreover, the route offers great potential for delivery of cytotoxic agents and therefore the attention has focused on to the development of oral dosage forms for chemotherapy in oncology.

Future Prospects of Nanomedicines

Herbal remedies and nutraceuticals products research are more familiar worldwide. The development of Phyto medicine in the drug delivery system in a number of organizations is being carried out at basic and clinical trial level²⁸. To improve the proper delivery systems at the sites or locations in the whole body in a particular dose will not compromise with the existing treatment²⁹. This would not only give relieve from unwanted effects such as toxicity and hypersensitive reactions but



also will increase the patient's strength internally is very much confidence boosting which is desirable. In the future, the concept of herbal nanoparticles for the treatment of critical diseases such as cancer, diabetes mellitus, and anemia drug delivery may also fascinate some potential research groups and potentially create attention grabbing results³⁰.

Table1: Different Plants Used for The Synthesis of Silver Nanoparticles

Plants	Plant Part Used	SIZE (nm)	Shape
<i>Alternanthera dentate</i>	Leaves	50-100	Spherical
<i>Acorus calamus</i>	Rhizome	31.83	Spherical
<i>Boerhavia diffusa</i>	Whole plant	25	Spherical
Tea extract	Leaves	20- 90	Spherical
<i>Tribulus terrestris</i>	Fruit	16-28	Spherical
<i>Psoralea corylifolia</i>	Seed	100-110	Spherical
<i>Hevetia peruviana</i>	Latex	10-30	Spherical
Aloe vera	Leaves	50-350	Spherical, Triangular
<i>Nelumbo nucifera</i>	Leaves	25- 80	Spherical, Triangular
<i>Citrus sinensis</i>	Peel	10-35	Spherical
<i>Melia dubia</i>	Leaves	35	Spherical
<i>Centella asiatica</i>	Leaves	30-50	Spherical
<i>Abutilon indicum</i>	Leaves	7-17	Spherical
<i>Premna herbacea</i>	Leaves	10-30	Spherical

Conclusion

The topic of nanotechnology is one that is quickly growing and has a lot of potential applications in business, medicine, and cosmetics. In order to increase their use for biosensing, environmental remediation, disease detection, and many other applications, nanomaterials are functionalized with both organic and inorganic components. Future herbal medicines with better bioavailability profiles and lower toxicity may be created with the help of nanotechnology and traditional herbal medicine. Conversations about nanotechnology are venturing beyond the confines of academic discourse. Long since, however, nongovernmental organizations have responded; now, the social sciences are delving into the cultural phenomena of nanoparticles, expanding discourses and bringing nanotechnology into entirely new social realms.



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