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Nano-technology in herbal medicines: A review

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Abstract

Herbal medicines have been used from years throughout the world; especially in India, herbal medicines are in high demand. The use of herbal medicines has increased because of their ability to treat different diseases with fewer side effects. The development of novel drug delivery system (NDDS) is of considerable importance to overcome various constraints like poor bioavailability, *in vivo* stability, aqueous insolubility, intestinal absorption and unspecific site of action. The integration of the Nano science as a NDDS in traditional system of medicine enriches the potential of herbal drugs for treating chronic diseases such as cancer and ravaging diseases. The synthesis of nanoparticles can be achieved by adopting the novel methodologies such as Polymer nanoparticle, Magnetic nanoparticle and Metallic nanoparticle depending on characteristic of the nanoparticles. The advanced technologies will shed lights for characterizing the nanoparticles to determine the toxicity profiles for their physical and chemical properties. This review article will provide a brief discussion of Nanoparticles synthesis, characterization by various techniques for production and its future impact of nanotechnology on smart herbal drugs.

Keywords: Nanotechnology, Herbal medicine, NDDS- Novel Drug delivery System, Synthesis, Characterization

1. Introduction

Ayurveda is one of the ancient medical sciences practiced in India ^[1]. Herbal medicines have been recognised by physicians and patients due to their potential therapeutic effect and also their fewer side effects as compared to other medicines, ^[2, 3] at the same time it also increases the bioavailability ^[4] of the medicine. For a long time, herbal medicines were not considered for development of novel formulations due to lack of scientific justification and processing difficulties. The modern phyto-pharmaceutical research can solve the scientific needs of herbal medicines in developing novel drug delivery systems, such as nanoparticles, micro emulsion, matrix system, solid dispersion, liposomes and solid lipid nanoparticles. The complexity of active constituents makes the development of novel drug delivery system for herbal formulations very challenging. In most of the conventional dosage forms, only a limited amount of administered dose reaches the targeted site, while the majority of the drugs get distributed throughout the body depending on physicochemical and biochemical properties^[5,6] resulting in low therapeutic value.

Novel drug delivery system (NDDS) for herbal medicines includes targeted drug delivery, which reduces dosage frequency, increases the solubility and absorption whereas decreases elimination ^[7]. Among all the NDDS, Nanoparticles are considered to be an important one. Nanoparticle can be used to target the herbal medicines to individual organs which improve the targeted drug delivery, effectiveness and safety of the medicine. Figure No 1.

To emphasize more, Nanotechnology is the engineering and manufacturing of materials at the atomic and molecular level. Despite the size restriction Nanotechnology commonly refers to structures that are up to several 100 nm in size. It is the use and manipulation of matter at a tiny scale. At this size, atoms and molecules work differently, and provide a variety of surprising and interesting results. Nanotechnology and Nano science studies have emerged rapidly during the past years in a broad range of product domains. It provides opportunities for the development of materials, including those for medical applications, where conventional techniques may reach their limits ^[8].

2. Novel drug delivery system for herbal remedies: A need of the hour

NDDS is designed to overcome the drawbacks of the traditional herbal drug system due to its wide applications to mankind.

→ Nanoparticle can be used to target the herbal medicines to individual organ which improves the selectivity, solubility, drug delivery, safety, effectiveness and reduces the frequent dose.

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- The nanoparticle size drug delivery enhances the entire surface area of the drugs therefore allocating quicker dissolution in the blood.
- Reduction in toxicity while maintaining therapeutic effects.
- The enhanced permeation and retention of nanoparticles can cross Blood Brain Barrier (BBB).

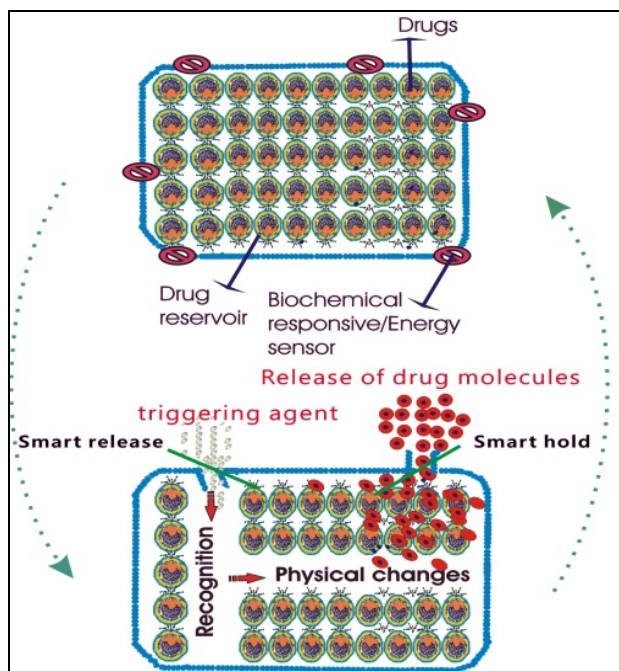


Fig 1: Release of drug molecules to the targeted site.

3. Nanoparticle synthesis

3.1 Polymer Nanoparticle

Polymer Nanoparticles are defined as solid, colloidal particles in the range of 10-1000 nm. Polymer Nanoparticle is known as nanosphere and nanocapsules. These can be prepared either from preformed polymers or by direct polymerization of monomers. Different methods like solvent evaporation, salting out, dialysis, supercritical fluid evaporation and rapid expansion of supercritical solution are being used [9]. The choice of preparation method is made on the basis of a number of factors such as the type of polymeric system, area of application, size requirement etc. The polymeric nanoparticles which are synthesized by any of these techniques are proved for efficient therapeutic activity. A schematic diagram represents (Figure No 2) how polymeric nanoparticles are synthesised.

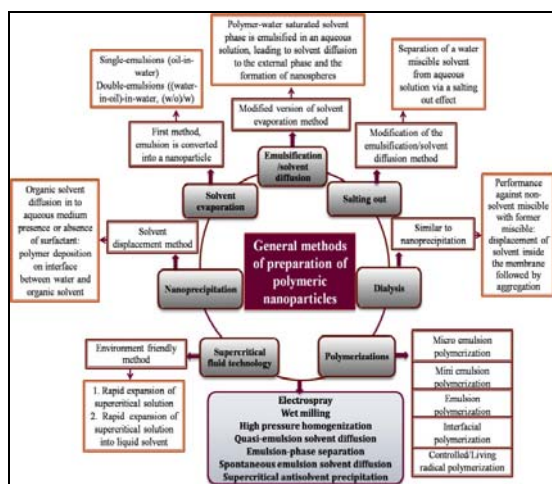


Fig 2: Schematic representation of various techniques for preparation of polymeric nanoparticles.

3.2 Metallic Nanoparticles

Metal nanoparticle is used to describe nanosized metals with dimension (length, width and thickness) range between 1-100 nm. There are various liquid phase methods for preparing metallic nanoparticles, such as chemical reduction, sol gel, and reversed micelle. Nobel metal Nanoparticles with spherical shaped and size, were produced continuously by the chemical reduction methods [10, 11]. In this schematic diagram represents how the metallic Nanoparticles has been synthesised by different methods shown in Figure No 3.

Metal nanoparticles are widely used due to their characteristic features such as large surface enriches, provides specific electronic structure between molecular and metallic states and process a large number of low coordination sites. These are used in magnetic separation of labelled cells and other biological entities, therapeutic drug, gene and radionuclide delivery, radio frequency methods for the catabolism of tumours via hyperthermia, and contrast enhancement agents for magnetic resonance imaging.

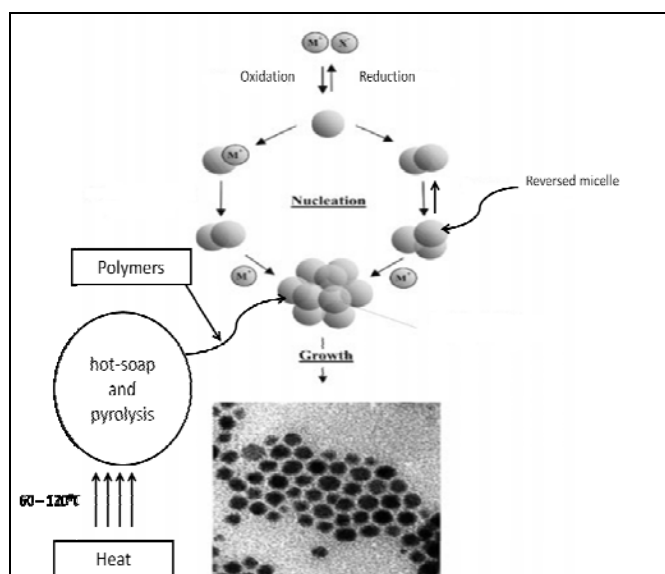


Fig 3: Schematic representation for preparation of metallic Nanoparticles.

3.3 Magnetic Nanoparticles

Magnetic Nanoparticles have been synthesized with number of different compositions and phases including pure metals like CO, Fe and Ni, metal alloys such as FePt, CoPt [12]. Using magnetic nanoparticles particle size of approximately 3 nm can be obtained. The size of particles will be hundreds of atoms which enable us to make recording media of up to 1 Tb/in² in recording density which can be achieved by correctly organizing the particles. Various methods are been reported few among them are coprecipitation, sonochemistry, colloidal method, solvothermal, combustion synthesis, hydrothermal method, microemulsion and thermal decomposition methods [13]. The key applications of MNPs are in Bio separation where the conjugation of the target biomolecules and MNPs which are functionalized with specific receptors, forms complexes and can be easily attracted by the applied magnetic field and extracted from the pristine mixture, thus providing a convenient and time-saving approach for bioseparation as compared to conventional method like centrifugation and filtration. This technology is also used in biosensing, drug delivery, magnetic resonance imaging and hyperthermia [14]. Figure No 4.

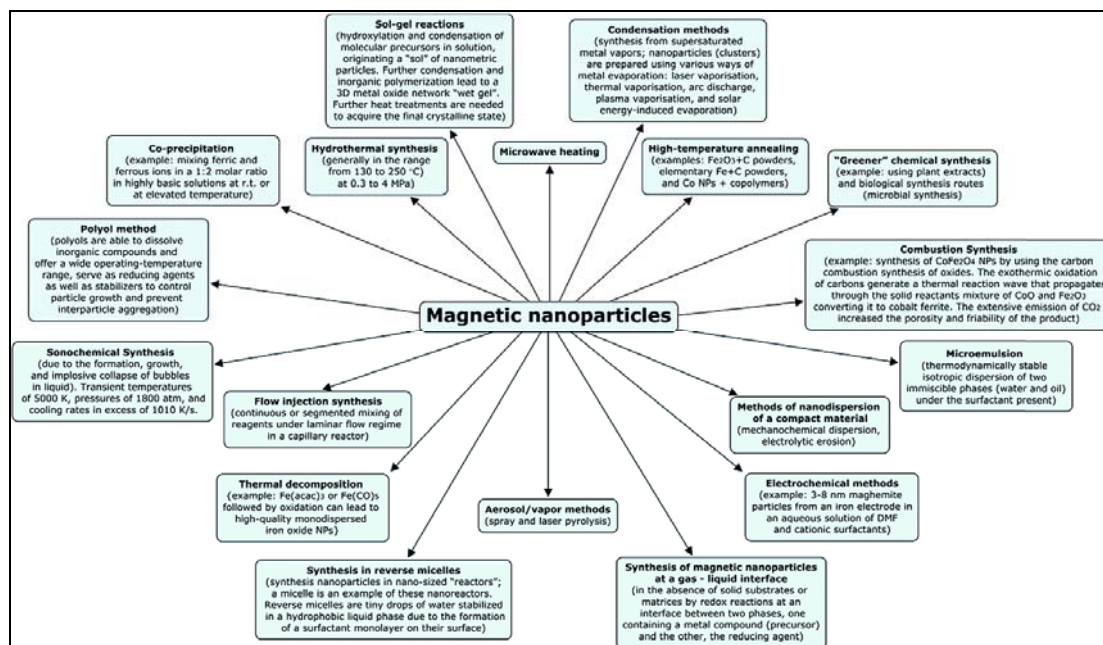


Fig 4: Schematic representation for preparation of Magnetic Nanoparticles.

4. Characterization of Synthesised Nanoparticles

Characterization refers to study of materials in its physical and chemical properties, composition and structures.

Nanoparticles are generally characterized by their size, morphology and surface charge, using advanced microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). Electron microscopy techniques are very useful in ascertaining the overall shape of polymeric nanoparticles, which may determine their toxicity. The surface charge of the nanoparticles affects the physical stability and redispersibility of the polymer dispersion as well as their *in vivo* performance.

4.1 Scanning electron microscope (SEM)

Scanning electron microscopy (SEM) is giving morphological examination with direct visualization. The technique is based on electron microscopy in which we used for morphological and sizing analysis; however, they provide limited information about the size distribution. For SEM characterization, nanoparticles solution should be first converted into a dry powder, which is then mounted on a sample holder followed by coating with a conductive metal, such as gold, using a sputter coater. The sample is then scanned with a focused fine beam of electrons. The surface

Characteristics of the sample are obtained from the secondary electrons emitted from the sample surface. The nanoparticles must be able to withstand vacuum and electron beam which can damage the polymer. The mean size obtained by SEM [15] is comparable with results obtained by dynamic light scattering.

4.2 Transmission electron microscope

The sample preparation for TEM [15] is complex and time consuming because of its requirement that sample should be ultra-thin for the electron transmittance. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles withstand the instrument vacuum and facilitate handling, they are fixed using either a negative staining material, such as phosphor tungstic acid or derivatives, uranyl acetate or by plastic embedding. Alternate method is to expose the sample to liquid nitrogen temperatures after embedding in

vitreous ice. The surface characteristics of the sample are obtained when a beam of electrons is transmitted through an ultra-thin sample, interacting with the sample as it passes through.

4.3 Particle size analyzer

Particle size distribution and morphology of the Nanoparticles are most important parameters for characterization of synthesized Nanoparticles. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affects the drug release, smaller particles offer larger surface area as a result, most of the drugs loaded onto them will be exposed to the particle surface leading to fast drug release. Whereas other side, drugs slowly diffuse inside larger particles. As a drawback, smaller particles tend to aggregate during storage and transportation of Nanoparticle dispersion. Hence, there is a compromise between a small size and maximum stability of Nanoparticles [16].

4.4 Dynamic light scattering (DLS)

Currently most popular method of determining particle size is photon-correlation spectroscopy (PCS) or dynamic light scattering (DLS). DLS is widely used to determine the size of Brownian nanoparticles in colloidal suspensions in the range of nano and submicron. A shining monochromatic light (laser) onto a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particle, changing the wavelength of the incoming light [17].

4.5 Atomic force microscopy (AFM)

AFM offers ultra-high resolution in particle size measurement and is based on a physical scanning of samples at sub-micron level using a probe tip of atomic scale. Samples are usually scanned in contact or noncontact mode depending on their properties. In contact mode, the topographical map is generated by tapping the probe on to the surface across the sample and probe hovers over the conducting surface in non-contact mode. The prime advantage of AFM is its ability to image non-conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures [18]. AFM provides the most accurate description of size and size distribution and requires no mathematical treatment [19].

4.6 Surface area analysis

The specific surface area of the particles is the summation of the areas of the exposed surfaces of the particles per unit mass. There is an inverse relationship between particle size and surface area. Nitrogen adsorption can be used to measure the specific surface area of a powder. The method of Brunauer, Emmett, and Teller (BET) is commonly used to determine the total surface area [20]. If the particles are assumed to be as spherical and in a narrow size distribution, the specific surface area provides an average particle diameter in nanometer as

formula below:

$$dBET = 6000/\bar{n}s$$

Where, S is specific surface area in m²/g
 \bar{n} is the theoretical density in g/cm³

In the present article the role of Nanoparticles for production of herbal formulations, medicinal uses of specific drug to improve the bioavailability and more therapeutic effect [21]. Different Nanoparticle formulations and their pharmacological action have been discussed in Table No 1.

Table 1: Nanoparticles formulations and their pharmacological actions.

SL No.	Nanoparticle Name	Functionalization	Uses	Method of synthesis	Reference
1	Curcumin	Anticancer	Potent Anticancer and Antitumor.	Wet-milling technique.	[22,23,24]
2	Paclitaxel	Antineoplastic	Acts against several tumours, ovarian and breast cancers.	Nanoprecipitation.	[25,26,27]
3	Berberin	Anticancer	Inflammation and several cancers.	Emulsion, Ionic gelation.	[59,60,61]
4	Camptothecin	anticancer	Potent anticancer	Encapsulated with hydrophobically modified glycol.	[28]
5	Ginkgo biloba	Alzheimer's dementia	Acts against loss of memory, thinking, language, behaviour.	Combination of Dry and wet process. (Gas-phase and liquid-phase grinding)	[29]
6	Triptolide	Anti-arthritis	Inflammatory and autoimmune diseases, especially for rheumatoid arthritis.	Nano encapsulation	[63,30,31,64]
7	Salvia miltiorrhiza	Anti-hyperlipidaemia	Cerebrovascular diseases, improve blood stasis.	Phospholipid complex loaded.	[32,33,34,65]
8	Quercetin	Anti-oxidant	Potent anticancer	Gelatin and chitosan loaded.	[35,36,37]
9	Breviscapine	Anti-cardiovascular	Cerebrovascular and cardiovascular diseases also against pulmonary fibrosis.	Lipid encapsulation.	[38,39,40]
10	Naringenin	Antioxidant, Anti-inflammatory.	Acts against several tumours and hepatoprotective.	Nano precipitation.	[42,43]
11	Dodder	Antioxidant	Acts against carcinogenesis and ageing also used as hepatoprotective.	Nano precipitation.	[44,45,46]
12	Silymarins	Hepatoprotective	Several liver diseases, breast cancer.	Cold homogenization.	[47,48,49]
13	Genistein	Antioxidant	Used in cardiovascular diseases, breast and uterine cancer also in osteoporosis.	Nano emulsion and chitosan microsphere.	[50,51]
14	Centellaasiatica	Anxiolytic	Acts as anti-anxiety, also used in leprosy, cancer, syphilis and allergy.	Ionic gelation.	[52,53,54]
15	Annual mugwort	Antimalarial	Also used for Asthma	Hydrophilic encapsulation.	[55,56]

5. Advantages of Nanoparticles

Significant advantages of Nanoparticles are given below,

- Increase bioavailability
- Dose proportionality
- Smaller dosage form
- Less toxicity
- Reduction in fed or fast variability

6. Health Implications of Nanoparticles

Nanoparticles can enter the human body in several ways, via Lungs where a rapid translocation through the blood stream to the vital organs is possible including the Blood Brain Barrier (BBB) and absorption by Intestinal tract and Skin [41].

7. Future prospect of Nano sized Herbal medicines

Nanosized herbal medicines can potentially enhance the biological activity and overcome the problems associated with pure herbal drugs. New challenges in the development of nanotechnology based drug delivery system include the feasibility of scale up process that bring innovative therapeutic

techniques to the market quickly, and the possibility of obtaining multifunctional systems to fulfil several biological and therapeutic requirements. Nanoparticles may exert toxicological effect; nanotoxicology has emerged as a new branch of toxicology for studying undesirable effect of Nanoparticle. In the past, health innovations were evaluated on their efficacy and improved patient quality of life. Currently, health care costs must also be considered. Nanotherapeutic products, which are more complex in structure and more expensive than conventional alternatives, are designed to provide an overall reduction in health care costs [57]. This reduction in health care costs is likely to be obtained by increasing the nanotherapeutic efficacy, reducing the length of in-patient stay, reducing personal health care costs, and the effective treatment of expensive major diseases.

The nanomedicine-related drug market is directly affected by the pharmaceutical regulatory environment, health care policies, demographics, and the wider economic environment. Companies specializing in nanomedicine have employed specific strategies to meet the challenges of this highly

competitive market. According to the BCC Research report [58], the market value of the worldwide nanomedicine industry was US\$43.2 billion and US\$50.1 billion in 2010 and 2011, respectively, and is estimated to reach US\$96.9 billion by the year 2016. The market for central nervous system products was valued at US\$11.7 billion and US\$14.0 billion in years 2010 and 2011, respectively. The market value is expected to reach US\$29.5 billion by the year 2016. The market for anticancer products was valued at US\$4.7 billion in the year 2010 and US\$5.5 billion in the year 2011, and it is anticipated to reach US\$12.7 billion by the year 2016. Considering the research efforts and the increasing investments in nanotherapeutics, the EU health care systems will likely be confronted with an increasing number of new nanomedicine products. The incorporation of nanotherapeutic products into national drug reimbursement strategies will have a strong impact on their availability throughout health care systems. As bio environment is already polluted with Nanoparticles of particulate matter, caution should be taken to prevent any environmental hazard by intentionally generated nanomaterials. Some additional new challenges include probing the targeting efficiency of Nanoparticles, and satisfying international standards for their toxicology and biocompatibility.

In the future, nano pharmaceuticals may alter the human body in the ways that we cannot imagine now but it is essential to consider benefits and side effects of the use of Nano Pharmaceuticals.

8. Conclusion

Herbal drugs have been recently getting more attention because of their potential to treat almost all diseases. However, several problems such as poor solubility, poor bioavailability, low oral absorption, instability and unpredictable toxicity of herbal medicines limit their use. In order to overcome such problems, nanoparticles can play a vital role. Hence, different nanoparticles show potential utilization to deliver herbal medicines with better therapy. In present review, the synthesis method of nanoparticles and characterization of nanoparticles are studied and plant and its parts or their product have been reported or utilized as anticancer, antioxidant, anti-anxiety, anti-malarial, liver and kidney tonic and also for cardiovascular diseases. These medicinal properties attributed by metabolites like saviarolic acid B, triptolide, ginkolic acid and paclitaxol, etc. However, many herbal drugs possessed poor aqueous solubility, physical instability, low absorption, lower bioavailability and slow pharmacological actions. To overcome these disadvantages, drug delivery systems that contain nanocarriers have been developed. Nano-coating herbal drug were produced by using various methods like homogenization technique, sequential simplex optimization, solvent evaporation method and wet and dry precipitation technique etc. Because of their small size and high surface area to volume ratio, nanoparticles drug carriers improves pharmacokinetic and bio-distribution of therapeutic agent. Other than their site specific action they can bypass blood barrier, improve the solubility of hydrophobic compounds as well as increase their stability.

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10. Footnotes

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