

Application of Nanotechnology in *Rasaushadhi* Preparations for Nanoparticle Synthesis—A Comparative Review

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Abstract

Nanotechnology—a constantly evolving branch of science and technology—reveals great potential for the early diagnosis, care and mitigation of numerous illnesses. In the field of Ayurvedic medicine, a variety of herbal, herbo-mineral and herbo-metallic compositions are used in formulations namely Bhasma, Kupipakwa Rasayana, Kharaliya Rasayana since a long era. To minimize the particle size of the substance (nanoparticles), procedures such as Shodhana, Nirvapa, Mardana, Bhavana, Marana, and others are carried out. These techniques not only eliminate the untoward effects of the metals but also transform them into biologically and physiologically active nanoparticles. So, the present study was aimed to review the comparison of various ancient technique used for manufacturing of Rasaushadhi for nanoparticle synthesis through the application of nanotechnology. Nanoparticles are the technological breakthrough of the century—a marvel with its tremendous surface area and ability to reach specific sites owing to their micro size have opened up novel applications in biological, optical, and electronic sectors among others. Since nanoparticles are small enough to contain electrons and create quantum effects, they frequently have unexpected optical features. On the other hand, the ancient discipline of Ayurveda has long recognised the use of nanometal particles. First reference regarding converting metals into nanoparticle is mentioned by Acharya Charaka (4th A.D.). Many studies done on Bhasma revealed that most of the Bhasma particle size comes under the range of nanoparticle (< then 100 nm). So, we can conclude that ancient knowledge of Ayurvedic manufacturing method covers the current scientific validation of nanotechnology principle and can prove an efficient therapeutic cure.

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INTRODUCTION

Nanotechnology is the 21st century's most advanced scientific technology. The Greek word "nanos," which meaning "dwarf (small)," is where the name "nanotechnology" originates [1]. At Tokyo Science University, Norio Taniguchi initially presented the idea of contemporary nanotechnology in 1974 [2]. It aims to develop nanoparticles, devices and dosage which covers the diverse area of matters at least any one dimensions in the range of 1–100 nm which can be increased up to 1000 nm.

Nanoparticles are a miracle invention of the century due to extremely small size, high surface area and targeted site action widely applicable in

various fields such as biomedical, optical and electronic etc. They typically have an unexpected property because they are small enough to contain their electrons and produce quantum effects. However, the ancient science of Ayurveda has been employing nanometal particles since 600–1000 BC [3]. In order to prepare *Lohadi Rasayana/Ayaskriti*, purified iron is heated up to red hot and then quickly quenched in appropriate liquid media immediately until flakes of iron become finely powdered [4].

Afterwards the emergence of Rasashastra (7th century AD), a number of new pharmaceutical processes were created, including *Shodhana* (purification), *Mardana* (trituration), *Jarana* (intermediate process), *Bhavana* (wet grinding), and *Marana* (incineration), which enable the transformation of metals and minerals into very fine, absorbable, therapeutically most effective and least or nontoxic form of medicines. The aim of present study was to compare different ancient techniques used for manufacturing of *Rasaushadhi* for nanoparticle synthesis with the application of nanotechnology.

MATERIALS AND METHOD

The data related to manufacturing process of *Bhasma* and *Kupipakwa Rasayana* from the classical literature, various research papers and material available on website have been collected and critically analysed.

RESULTS

Methods for Creating Nanoparticles as per Ayurveda

Various herbs, metal and minerals are used internally as medicine since a long era. As per the need of time, they are processed or converted into various dosage form such as *Bhasma*, *Ayaskriti*, *Kupipakwa Rasayana*, *Parpati*, *Pottali*, *Asava-Arista*, *Kshara* and many more for easily administration and targeted site action of drug delivery system.

Lohadi Rasayana/Ayaskriti

For the preparation of *Loha Rasayana*, *Teekshna Loha Patra* are heated to red hot by application of strong heat and then dipped in liquid media of *Triphala Kwatha*, *Gomutra*, *Jyotishmati Ksharodaka*, *Ingudi Ksharodaka*, and *Palasha Ksharodaka*, respectively till it becomes *Anjanvata* [4]. Acharya Sushruta has mentioned *Ayaskriti* preparation in which smearing of *Lavana* paste on *Tikshna Loha*, then heated red hot and dipped in liquid media repeatedly for making fine powder [5].

Bhasma

Bhasma is a sort of medicine that deals with metals and minerals in order to make treatment more effective in lower therapeutic dose and acceptable taste. In the preparation of *Bhasma*, various processes such as *Shodhana*, *Jarana*, *Marana*, *Bhavana*, and *Putapaka* are involved which is meant to bring down the particle size more in finer form.

1. *Shodhana* – It is the first step involved in the preparation of *Bhasma*. It is a process by which various impurities get separated from substances. There are different techniques used for *Shodhana* such as *Avapa*, *Nirvapa*, *Mardana*, *Dhalana* etc.
 - *Nirvapa* - In this process, repeated heating and quenching of drug in liquid media is done. It causes brittleness, breaking and size reduction of the metals and minerals.
 - *Mardana* - In this process, the material is continuously ground for a specific period of time to convert into very fine powder.
2. *Jarana* – It is a transitional process for low melting point metals. In these, metals are molten and rubbed by particular plant drug powders with the help of iron ladle until metals change to complete powder form.
3. *Bhavana* - The intermediary step between *Shodhana* and *Marana* is called *Bhavana*, and it involves wet grinding. As it also aids in the reduction in size of mineral and metal particles so they can transform into organometallic complexes.

4. *Marana Dravya* – To prepare *Bhasma*, different *Marana Dravya* such as *Parada*, *Gandhaka*, *Hartala*, *Manahsila*, *Ariloha*, and herbal drugs are used to rapidly dissolve metal and mineral particles.
5. *Putapaka* – It is a process in which specific quantity of heat is applied for repeated times for converting the metals and mineral into *Bhasma* (fine powder) form.

The *Marana* process converts the macro- and micro-forms of minerals and metals into forms that are far more beneficial for medical purposes. *Bhasma* attains such a fine form that it is able to absorb in the body at cellular level and shows definite therapeutic effects. Certain parameters such as *Varna* (color), *Varitara* (lightness), *Rekhapurnatwa* (fineness), *Dantagre na Kach Kach Bhavati* (no sound crushing between teeth), *Lochanaanjana sannibha* (collyrium like), *Apunarbhava* (irreversible state), and *Gata Rasatva* (no metallic taste) [6] are given for the assessment of good quality of *Bhasma* which indicates its fineness, lightness and softness. Many research works have been carried out in which *Bhasma* is analyzed for particle size through various tools and techniques such as Atomic Force Microscope (AFM), Transmission Electron Microscope (TEM), Scanning Electron microscope, and Energy Dispersive Spectroscopy (SEM- EDS). The particle size was found under nonorange as mentioned in Table 1.

Kupipakva

The process of *Kupipakva* involves grinding the purified metals and minerals together producing *Kajjali*, which is often a dark tint. Then kept at the bottom of a bottle with a short neck that has been thoroughly covered with a layer of cotton and mud mixture. The bottle without a cork is maintained in a specific temperature by customized *Bhatthi* (electric muffle furnace) so that the area below the neck remains covered but the neck is left exposed to the air. After that product is sublimated as a result of a strong fire being used to well-sealed cork. On self-cooling the bottle is broken carefully into two pieces and grinded well obtained material which is known as *Kupipakva Rasayana*. The particle size of various *Kupipakva Rasayana* such as *Rasa Sindoor* [19] and *Tamra Sindoor* [20] are analyzed in the range of 118–138.2 nm at a magnification of 20 kX and 486.3 nm, respectively. Similarly, the research works carried out on the mean particle size of *Agnikumara Rasa* [21] and *Khagesara Rasa* [22] found that they were at 21.18 nm, 7kX and 281–335nm range, respectively.

Pottali

In *Pottali Kalpana*, a consolidated type of mercurial preparation where sulphur and mercury amalgam are treated with various plant components before being applied to a natural binder to give the mixture a compact form. A mean particle size of 317.1 nm is found in *Rasagarbha Pottali* [23].

Table 1. Particle size of various *Bhasma* analyzed in nanoparticle range.

| No. | <i>Bhasma</i> | Size |
|-----|------------------------------------|------------|
| 1. | <i>Abhraka Bhasma</i> [7] | 100–200 nm |
| 2. | <i>Lauha Bhasma</i> [8] | 50–100 nm |
| 3. | <i>Tamra Bhasma</i> [9] | 2.2 nm |
| 4. | <i>Swarna Makshika Bhasma</i> [10] | 50–200 nm |
| 5. | <i>Swarna Bhasma</i> [11] | 5657 nm |
| 6. | <i>Rajata Bhasma</i> [12] | 2.7 nm |
| 7. | <i>Yashada Bhasma</i> [13] | 324 nm |
| 8. | <i>Naga Bhasma</i> [14] | 60 nm |
| 9. | <i>Vanga Bhasma</i> [15] | 50–300 nm |
| 10. | <i>Trivanga Bhasma</i> [16] | 500 nm |
| 11. | <i>Mukta Bhasma</i> [17] | 156 nm |
| 12. | <i>Shankha Bhasma</i> [18] | 600 nm |

Methods for Creating Nanoparticles as per Modern Medicine

In order to create nanoparticles, the bottom-up manufacturing concept is used, which entails building up the atom or molecular constituents as opposed to the top-down method, which includes etching smaller and smaller shapes from the bulk material [24]. Various methods included for synthesis of nanoparticle are as follows [25]:

1. *Physical Methods* – It includes attrition, thermal decomposition, pyrolysis and laser ablation.
 - *Attrition*- This technique uses a ball mill, planetary ball mill, or other size-reducing device to grind up macro- or micro-scale particles.
 - *Thermal Decomposition* - A reactant can produce two or more products when certain substances undergo thermal breakdown. When exposed to heat, many metal carbonates, such as copper carbonate, decompose readily.
 - *Pyrolysis* - High pressure is used to push a liquid or gas that is the precursor of vapour through an aperture or hole and burn it. In order to recover oxide particles from by-product gases, the resulting solid is categorised as air. Particles that have undergone pyrolysis frequently cluster and clump together.
 - *Laser Ablation* - With this technique, a solid metal rod is ablated in an Ar gas-filled chamber using a high-power Nd:YAG laser. Metal atoms evaporate and condense on a water-cooled substrate within the plasma produced by laser ablation. It works with transition metals and elements with high melting points.
2. *Chemical Methods*: It includes solgel, chemical vapour deposition, sono-chemical, and hydrothermal methods.
 - *Solgel* - It consists of the solution-borne condensation, hydrolysis, and thermal breakdown of metal alkoxides or precursors. The creation of a stable solution, or sol, is the outcome. Increased viscosity is created in the gel upon hydrolysis or condensation. By adjusting the pH, temperature, and precursor concentration, the particle size can be observed.
 - *Chemical Vapour Deposition* - In a reaction chamber, a thin film of gaseous reactant is deposited on the substrate and chemical reaction take place as combining gas in contact with heated substrate. The consequence of this reaction is a thin layer of product on the substrate's surface.
 - *Sono-chemical*- Pd-CuO nanohybrids have been successfully created by sono-chemically fusing copper salt with palladium in the presence of water. When switch metal salts are combined with water and palladium, they can be converted into their oxides using ultrasonic vibrations.
 - *Hydrothermal*: This type of synthesis employs a wide range of temperatures, from room temperature to very high temperatures, to create nanoparticles.
3. *Biological Method (Green Synthesis Method)* - The process entails the bioreduction of metal ions into a cluster of crystallites, which are subsequently stabilised by reactive phytochemicals derived from plant extracts or microorganisms such as fungi, bacteria, algae, or enzymes, as well as agricultural waste. Metal salts split off into hydroxyl complexes and positive metal ions. The hydroxyl complexes are decreased and the metal crystallite planes begin to grow when the plant extract is gradually introduced to the metal salt solution. High-energy crystallite planes are capped by secondary metabolites possessing free activation energy and a compatible opposite charge.

DISCUSSION

Bhasma as a Nanoparticle

It is evident from seeing the various phases of *Bhasma* preparation that efforts are made to reduce the particle size at each stage to an ever-finer degree.

Role of *Shodhana* in Particle Size Reduction

Shodhana processes such as *Nirvapa* causes size reduction which can be explained by:

1. *Griffith Theory* [26] – Microscopic fractures and fluxes are present in all substances. Any structural defect that could crack under stress, such as heat, is called a flow. The higher part of

the surface receives the initial force application in the form of heat. This causes the bonds to weaken, which could be the cause of the flaws. The particle that has the weakest flow breaks the easiest and creates the biggest pieces. Another weakest flow cracks on the subsequent stage. Particle size is decreased in this way.

2. *Stress corrosion cracking theory* [27] - It is the result of a material cracking either trans- or intergranularly as a result of tensile stress and a particular environment. When typically ductile metals are subjected to tensile stress, it might result in an unexpected, rapid failure, particularly when the metal is exposed to elevated temperatures. Stress corrosion cracking is highly chemically specific means specific metals are cracked by attack of specific solutions either acidic or alkaline media.
3. *Phenomenon of Hydrogen Embrittlement* [28]- In this phenomenon, atomic hydrogen which ingresses into the metal or alloy during various processes reduces the ductility and load bearing capacity causing cracking and brittle failure. In relation to *Nirvapa* procedure, hydrogen produced by corrosion reactions may enter the metal in atomic form leading to increased brittleness of metals.

Role of *Jarana* Process in Particle Size Reduction

Metallic materials undergo oxidation when heated in open air, raising the metal's melting point and enabling particle size reduction [29].

Role of *Marana Dravya* in Particle Size Reduction

Since *Marana Dravya* has an acidic and basic character, it helps the herbal medications dissolve metal and mineral particles more quickly. Mercury, on the other hand, is meant to amalgamate with any metal and disintegrate or disperse its particles to the smallest subdivisions [30].

Role of *Bhavana* in Particle Size Reduction

By the process, the *Bhavya Dravya* in the *Bhavana* breaks into tiny particles and loses its molecular cohesion. As per "Attrition theory," because of rubbing mortar and pestle along with the pressure during the process results in particle size reduction. Further enhancing the breakdown of molecules is the vibratory movement and weight of the pestle. So, during *Bhavana*, drug particles are exposed to a variety of stressors that cause chemical bonds to break and form new surfaces. These breaks also cause the re-joining of the fractured surfaces to be delayed, which results in particle size reduction [31]. It is recommended to include liquid medium in *Bhavana* to accelerate the size reduction process even more [32]. Wet grinding helps move drug material between grinding surfaces and aids in the following proliferation and initiation of cracks that are followed by particle size reduction. It requires two simultaneous processes that is, pulp flow and stress application [33].

Role of *Putapaka* in Particle Size Reduction

Previous research indicates that when *puta* is administered in the appropriate quantum, there is a noticeable decrease in particle size after each and every *puta*. As the number of *puta* increases, the proportion of acid insoluble ash progressively drops and the percentage of acid soluble ash gradually increases, indicating a conversion to a more assimilatory form, according to a review of chemical analysis [34].

Products created using the aforementioned procedures also display the characteristics associated with nanoparticles. However, *Ayurvedic* techniques are rather archaic and may include a combination of nanoparticles and small particles. Attrition works incredibly effectively and is widely used in *Ayurvedic* pharmacies. It is suggested to grind more and more in order to increase the drug's effectiveness.

Research on green synthesis of nanoparticles is currently focused on the generation of nanoparticles that are free of hazardous chemicals, economical, and environmental friendly as compared to other physical and chemical methods that require high energy, a separate chamber, a lengthy process, and

some toxic hazardous materials [35]. Green synthesised nanoparticles have also demonstrated a variety of biological activities, such as anticancer, antioxidant, antidiabetic, and antibiotic properties; however, extensive studies must be conducted before using medications obtained through innovative and creative methods [36]. Though manufacturing of *Bhasma* is such a tedious work but their clinical and toxicity [37] data has proven their efficacy much more concern towards its standardization.

Since nanoparticles are biodegradable, biocompatible, and non-antigenic in nature, they play a critical role in the field of nanoscience. Applying them to the blood–brain barrier allows for the controlled, targeted and selective distribution of medications to a particular location of action. However, a number of studies on artificial nanoparticles carried out in the last several years have raised questions regarding their safety due to genotoxicity, inflammation, immunotoxicity, and carcinogenicity. Most of the nanoparticles that are ejected from the body wind up in the air and water, where they pose a risk to both individuals and the environment.

In this concern *Bhasma*, *Kupipakva* and *Pottali Rasayana* when analysed for its particle size, mostly falls under the range of nanoparticles along with the properties of non-toxic, easily absorbable, targeted drug delivery, and increased metabolism at cellular level. It also acts as a catalyst, immunomodulator, and anti-aging agents.

CONCLUSION

In the field of nanotechnology, nanoparticle synthesis has gained much importance due to its various applicability in diagnosis, drug delivery, and targeted therapy. The principles such as *Nirvapa*, *Mardana*, *Bhavana*, and *Marana* involved in the manufacturing of *Bhasma*, *Kupipakva Rasayana*, and *Pottali* can be compared with the scientific techniques of nanotechnology to create nanoparticles such as attrition, pyrolysis, sol–gel and others and eventually evolve as nanomedicine.

Conflict of Interest

None declared.

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Nil.

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