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Review Article

Nanoparticles, Precision Engineering for Synthesis of Tailored Dosage Form

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Abstract:

This review shows the most current approaches which are being used in the procurement, diagnosis, and therapeutics of multiple diseases parallel with inarguable barriers. NPs are progressing and has extended to multiple types for targeted drug delivery in recent years and act as a game changer in the modern medicines. With clinical uses ranging from contrast agents in imaging to carriers for medication and gene delivery into tumors, NMs have become crucial players in contemporary medicine. In some cases, nanoparticles (NPs) allow for tests and treatments that would not be possible without them. On the other hand, NPs also pose special environmental and societal problems, particularly in terms of toxicity. Therefore, clinical applications of NPs need to be reviewed, and a thorough comprehension of NP effects from the pathophysiologic basis of a disease may lead to more advanced diagnostic options, more productive therapeutics, and more effective preventative aspects. On the other hand, a list of methodologies has been discussed which are being employment for the formulation of these NPs which have affected and improved their physical and chemical characteristics.

Key Words: nanoparticles; drug delivery system; nanotechnology

Abbreviations:

NPs- Nanoparticles

MSM- Mesoporous silica material

CVD- chemical vapor deposition

CNTs- carbon nano tubes

Introduction

For several years, there has been considerable research interest in the domain of drug delivery using particulate delivery systems such as nanoparticles. Nanoparticles are primarily indicated when improving drug molecules' pharmacokinetic and pharmacodynamic properties is desirable. Nanoparticles are the fundamental units of nanotechnology. They can be defined as solid particles or particulate dispersions ranging from 10-1000nm. One can produce nanoparticles, nanospheres, or Nano capsules depending on the preparation technique. Nanospheres systems allow the drug to be physically and uniformly distributed in the matrix. In contrast, Nano capsules are systems in which the drug is contained in a cavity and enclosed by a unique polymer membrane.

They are microscopic particles with unique physical and chemical properties like Lower melting points, very large surface area, specific optical properties, mechanical strength, and specific magnetization. [2] Due to their unique properties, they are the most demanding in many fields like medicine, electronics, energy, and environmental remediation. For example, in medicine, they are used to deliver drugs at a specific site in the body.

But due to their very minute size, there are some potential hazards related to nanoparticles, as they can penetrate the cell membrane and interact with biological systems unexpectedly [2]. Nanoparticles offer unique advantages over conventional drug forms. The benefits of utilizing nanoparticles as potential drug delivery systems can be summarized below:

1. They have the ability to retard or control drug release during transportation and at the localization sites, resulting in improved drug distribution and subsequent clearance, which leads to an exponential increase in drug efficacy and a sharp decline in adverse effects.
2. Researchers can conveniently alter and modify nanoparticles' surface characteristics and particle size to achieve active and passive drug targeting after the parenteral administration.

3. Nanoparticles can achieve site-specific targeted drug delivery by introducing targeting ligands that attach readily to particle surfaces or through magnetic guidance [3].
4. Researchers can easily adjust controlled release and particle degradation properties by selecting the right matrix components.

Despite these advantages, Nano-particles still have some drawbacks. Their small size promotes particle-particle aggregation, making them difficult to handle in liquid or dry form. Being tiny also means there is only limited drug loading and release.

Researchers must address these issues and limitations before nanoparticles can truly replace conventional drug forms. Research is ongoing to identify further health and environmental risks and use nanoparticles safely and effectively. The present review details the introduction of the nanoparticle drug delivery system and the latest developments, types, and potential applications of nanoparticles.

2. Classification of nanoparticles.

Nanoparticles are classified into various types on the basis of their various properties. Some of them are

2.1. Exosomes.

Exosomes are biological, spherical, lipophilic, bilayer vesicles. They are considered a type of nanoparticle due to their small size. Their size is very small, ranging from 40nm to 100nm [4]. Due to their unique properties, they are used as a vehicle to deliver drugs and other therapeutic agents. They are biocompatible and are used for targeted drug delivery to a specific cell or tissue. They are lipophilic in nature and can cross biological barriers like Blood Brain Barrier, so they are used in neurological diseases. They are used for targeted drug delivery in diseases like cancer. [5] They are used to deliver those drugs to the target via multiple pathways that are deactivated or degraded when administered alone [6]. They have low immunogenicity and can be modified to target specific cells or tissues, which reduces the potential for off-target effects.

The drug is loaded into the particle and is delivered to the target site. The drug is loaded via multiple techniques, including Active loading and passive loading. In Passive loading, the drug is incorporated into the particle via the diffusion method. This method has limitations and poor drug-loading capability. This method is not suitable for all types of drugs. As they are lipophilic in nature, so only drugs that are lipid soluble in nature can be incorporated via the Passive loading technique.

2.2. Liposomes:

Liposomes are drug vesicles that are based on phospholipids with diameters ranging from 0.5 to 5.0μm [7]. They have the ability to form multiple bilayers resulting in an enclosed central aqueous compartment. Liposomes are being widely investigated ad delivery vehicles for imaging agents, proteins, and molecular drugs. They have a high success rate in the domains of food and cosmetics

Liposomes range from 30nm to several micrometers, with the bilayer being approximately 4-5 nm thick. Liposomes are excellent drug delivery systems due to numerous reasons.

They protect the encapsulated drug from physiological degradation and help to extend the half-life of the drug. In addition, liposomes enable researchers to control the release of drug molecules. Perhaps the biggest advantage of liposomes is that they allow for passive and active targeted drug delivery, drastically reducing the systemic side effects by increasing the threshold for maximum-tolerated dose and improving the therapeutic effect [8].

Despite numerous perks, only 14 types of liposomal products are available on the market. This is due to the several limitations these drug delivery systems pose. Liposomes are not suitable carriers for drugs with high molecular weight and solubility. Furthermore, liposomes are highly unstable under mechanical stress and high temperature, which can lead to drug leaking and degradation. Lastly, liposomes are considerably expensive dosage forms and can elicit an immune response, leading to a greater side effect profile. researchers need to address these limitations before liposomes can be used to a greater extent.

2.3. Metallic Nanoparticles:

Metallic nanoparticles (NPs) are tiny metallic particles ranging from 1-100 nanometers. They comprise various metallic elements such as gold, silver, iron, and platinum. Metallic NPs have shown tremendous potential for drug delivery and imaging in medicine.

These particles have benefits as potential drug delivery systems. They offer a large surface area to volume ratio, drastically increasing drug absorption. In addition, they can be conjugated with various ligands like peptides or antibodies for targeted drug delivery to the site of action. Furthermore, metallic NPs exhibit excellent optical properties, which researchers can exploit for imaging applications.

Gold nanoparticles can enhance the contrast of X-ray CT and MRI scans. Metallic nanoparticles also have antimicrobial and anticancer properties. [9] Despite their numerous perks, they still have limitations preventing them from being commercialized readily [10]. The biggest concern regarding metallic nanoparticles is their potential for causing toxicity. research shows that metallic NPs can accumulate in various body organs and exhibit toxicity and inflammation. These particles can also agglomerate and degrade over time, reducing efficacy. these limitations need to be addressed before metallic NPs can be commercialized.

2.4. Polymeric Nanoparticles

Polymeric particles are Nano-scale particles with diameters ranging from 10-1000nm, made from either synthetic or natural polymers. These particles have gained immense traction for their potential application as drug delivery systems and imaging aids [11].

Polymeric nanoparticles offer several advantages over conventional drug delivery systems. These particles offer sustained drug delivery, extending the therapeutic effect of various drugs. In addition, polymeric nanoparticles protect drug molecules from premature degradation by increasing their solubility, resulting in improved bioavailability.

These nanoparticles can also reduce drug toxicity and side effects by limiting drug exposure to healthy tissues. Lastly, these nanoparticles are highly versatile and diverse. They can be readily modified with numerous functional groups enabling them to be used in drug delivery, medical imaging, and food technology.

Despite numerous benefits, these particles have their fair share of disadvantages. Polymeric nanoparticles are prone to aggregation and degradation under mechanical stress, reducing their long-term efficacy. Furthermore, these particles are unsuitable for high drug doses because they have limited loading capacity. These issues need to be addressed before they can be commercialized readily.

2.5. Dendrimers

Dendrimers are highly-branched and symmetric macromolecules on the nanoscale. they have highly specialized, three-dimensional structures that consist of an inner and outer shell with surface functionalities and applications in medical imaging and drug delivery.

Dendrimers have a high success rate in drug delivery and medical diagnosis. They can encapsulate and release drug molecules in a

controlled manner, and their surface can be conjugated with various chemical moieties to achieve targeted drug delivery. In addition, dendrimers are highly biocompatible and easily eliminated from the body. They also have low toxicity potential and immunogenicity, making them ideal diagnostic and therapeutic tools. Lastly, Dendrimers can be labeled with various imaging agents making them useful in MRI and fluorescence imaging. [12]

Despite several benefits, they have numerous disadvantages that prevent their commercialization. Dendrimers use complex and time-consuming processes, dramatically driving their costs. Despite the potential for low toxicity, several dendrimers are extremely toxic. Therefore, careful selection of these particles needs to be done.

2.6. Nano emulsions

Nano emulsions are colloidal dispersions of droplets in the 10 to 100-nanometre range. These droplets are stabilized with the use of surfactants. Nano emulsions have garnered tremendous attention over the past few years due to their applications in drug delivery and cosmetics.

They offer several benefits over conventional drug delivery systems. Nano emulsions can be designed to release drugs slowly and sustainably, leading to sustained drug plasma concentration and extended therapeutic effect [13].

In addition, Nano emulsions can increase the ability of drug molecules to traverse biological membranes, decreasing the required doses and increasing therapeutic efficacy. furthermore, these emulsions have improved stability due to smaller droplet size and greater surface area to volume ratio, which can lead to extended shelf life and improved drug bioavailability.

Lastly, Nano emulsions can improve the texture and overall look of drugs, making them more appealing to patients.

Despite many benefits, Nano emulsions have several limitations. These systems require high energy output during manufacturing, which can result in difficulty scaling the procedure. This drastically drives up the cost, making these drug delivery systems rare [14].

Numerous surfactants used to stabilize Nano emulsions exhibit a high degree of toxicity. Therefore, they should be analyzed carefully before incorporation. Perhaps the biggest hurdle in their commercialization is the lack of extensive research into Nano emulsions' long-term safety and efficacy. These limitations need to be dealt with before Nano emulsions can be readily commercialized.

2.7. Ethosomes

Ethosomes are lipid based vesicular carriers, made up of phospholipid, water, and alcohol and sometime glycol [15]. The phospholipid is made up of a hydrophobic head and two hydrophilic chains, due to which they are used to incorporate a large and diverse group of drugs. They are the modified form of liposomes and are often used in transdermal and topical preparations [16].

The alcohol in it acts as preservative and provide stability and protection to the drug from degradation. Alcohol also enhances the permeability of lipid bilayer so the drug is absorbed easily through the lipid bilayer.

The advantages of using Ethosomes in the drug delivery system are [17],

- Low risk
- High compliance
- High stability
- Enhanced solubility
- Easy to synthesize
- Delivery of large molecules (proteins, peptides etc.)

They are being studied for the treatment of skin disease like skin cancer, acne, and psoriasis. They have also been used in the cosmetic products like skin lightening and anti-aging formulations [18].

2.8. Mesoporous Silica Materials

Mesoporous silica materials are the ordered porous silica materials, with pore size ranging from 2-50nm, pore volume ca 1cm3 g-1, high surface area and chemical and thermal stability [19]. They are majorly composed of silica but can incorporate other materials like metals, organic molecules and polymers. Due to their ordered, homogenous porous structure, they are used as a carrier for various types of drugs, such as small molecules, proteins, peptides, nucleic acids. They are used for targeted drug delivery and due to their ordered, tunable structure, they provide controlled release of the drug thus enhance the therapeutic efficacy of the drug and reduce the toxicity [20].

They are used for the treatment of cancer, infectious disease, and different bone disease. They are biocompatible and biodegradable agents. They are converted into their metabolites which can easily be excreted via urine [21]. They protect the drug from premature release, so they are much beneficial for the drugs with shorter half-life.

MSM can revolutionize the drug delivery system. Research is needed to optimize the design and functionalization of these materials.

3. Synthesis of nanoparticles

Nanoparticles are synthesized by using various techniques. These techniques are classified into two types.

1. Top-down method
2. Bottom-up method

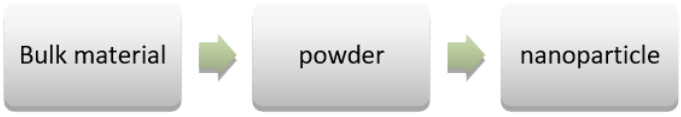
These methods are used widely to produce nanoparticles [22].

3.1. Top-down method

In top-down method larger particles i.e., bulk material is converted into smaller particles using different techniques such as

- Mechanical milling
- Nanolithography
- Laser ablation sputtering
- Thermal decomposition method
- Sputtering

These are the common methods which are used to convert bulk material into powder which is further processed to make nanoparticles. The diagram shows the Top-down approach of synthesis of nanoparticles,



3.2. Bottom-up method

In the bottom-up method of nanoparticle synthesis, the small particles (atoms) are combined to form large particles (Clusters), which are further combined to form nanoparticles. Different techniques are used to combine the small particles into larger ones.

- Sol-gelMethod
- Hydrothermal Method
- Electrochemical Deposition
- Chemical Vapour Deposition
- Pyrolysis
- Spinning

These are the techniques that are used to convert atoms into nanoparticles. The following chart shows the bottom-up approach of nanoparticle synthesis.

3.2.1. Sol-Gel method

It is the method of conversion of sol into the gel using chemical reactions. This method is commonly used to prepare metal oxide nanoparticles. These are the steps involved in this method.

- **Formation of SOL**

Metal salts or organic material are dissolved into the appropriate solvent. The solution formed contain compounds which act as a precursor of the nanoparticles.

- **Hydrolysis**

Water or hydrolyzing agent is added to the sol which cause the breakdown of the precursor molecule and a gel network is formed.

- **Condensation**

The hydrolyzed product undergoes condensation and small particles combine to form larger nanoparticles. Also, in this process water or other products are removed.

- **Aging**

The resulting network is allowed to ripen for a period. This process enhances the structural properties of the particle such as crystalline nature and uniformity.

- **Drying**

The gel is dried using different techniques, such as freeze drying.

- **Calcination**

The product formed is subjected to high temperature to remove any organic material present in it. This process promotes particle growth.

This method is economically feasible and controlled control over particle size and shape. These properties make it suitable for both laboratory and industry [23]

3.2.2. Electrochemical deposition

The Electrochemical deposition method is used to synthesize metallic nanoparticles. In this method, an electric current is passed through the electrolyte, and the metal ions are deposited on the cathode surface. Steps involved in this method are,

- **Preparation of electrolyte**

Metallic salts are dissolved in an appropriate solvent, and the electrolyte is prepared.

- **Electrochemical cell**

Cathode and anode are dipped into the electrolyte and a power source is connected to it.

- **Deposition**

Electric current is passed through the electrodes, and metal ions start depositing on the cathode. The nanoparticles are collected from the cathode surface.

This method is rapid, and no chemical reductant or oxidant is required. This method gives controlled size and shape of the product [24]. Also, there is absence of undesirable by products so this method is feasible for laboratories and industries.

3.2.3. The Hydrothermal method

This is the bottom-up approach to nanoparticle synthesis. In this method, the nanoparticle is prepared in the aqueous environment under high temperature and pressure [25]. Steps involved in this method are:

- **Solution formation**

The precursor solution is formed by dissolving metal salts or other chemical precursors in the solvent (which is mostly water) in which the precursor is readily soluble.

- **Packing and heating**

The reaction mixture is sealed in the pressurized vessel. The vessel is heated in the hydrothermal reactor. The reaction can take place under high temperatures and pressure in an aqueous environment. As the reaction proceeds, nucleation occurs which results in the formation of nanoparticles.

- **Cooling**

After the reaction time is completed, the vessel is allowed to cool at room temperature, resulting in stable nanoparticles.

- **Collection and purification.**

The particles are further collected from the reaction mixture via different processes like centrifugation, filtration or precipitation. They are further purified to remove impurities.

It is an environmentally friendly method as water is used as a solvent. Also, this method provides precise control over particle size and shape.

3.3.4. Chemical Vapor Deposition

In Chemical vapor Deposition (CVD), precursor gases essential to nanoparticle production are chosen. A reactor offers a regulated environment with a reaction chamber, heating element, and substrate. The breakdown or reaction of the precursor gas is triggered by heating the chamber. The gases adsorb on the heated substrate after diffusing there. Surface reactions create nucleation centers, and they develop into nanoparticles through processes including diffusion and coalescence. Precursor gases are eliminated when the required size and shape are attained, leaving nanoparticles on the substrate for collection. CVD has been successfully employed in nanoparticle production, such as synthesizing large-area graphene by chemical vapor deposition (CVD) of methane on Cu foils.[26]

The method consists of the following steps:

- **Selecting Precursor Gases**

This step involves choosing the appropriate gases containing the required elements or compounds for nanoparticle formation. The properties of newly formed nanoparticles depend upon the type of precursor gas used. Hence using various precursor gases can result in nanoparticles with distinct properties. [26]

- **Designing the Reactor**

In this step, the operator creates a controlled environment within the reactor which consists of a reaction chamber, a heating element, and the substrate. This enables the manipulation and modification of reaction conditions.

- **Heating and Activating the Reaction Chamber**

This step involves increasing the reactor temperature to enable the decomposition of precursor gases. Controlled temperature and decomposition ensure that desired reaction kinetics is achieved and undesirable side reactions are prevented. CVD is also employed in the synthesis of carbon nanotubes (CNTs). This step of heating and activating the reaction chamber is crucial. Therefore, the flow rate of hydrocarbon gases as well as the temperature should be accurately controlled so the precursors can be decomposed to provide reactive hydrocarbon for CNTs formation. [28]

- **Adsorbing Precursor Gases onto the Substrate**

Now, the precursor gases are allowed to flow into the reaction chamber and interact with a heated substrate. This enables them to diffuse and adhere to the substrate surface through the process of adsorption. Temperature, pressure, and substrate properties heavily influence this step.

- **Initiation of Nucleation**

Once the precursor gases have adsorbed onto the surface of the substrate, they undergo several chemical reactions, which lead to the formation of nucleation centers. These nucleation centers are the building blocks of nanoparticle growth and synthesis, and they involve precursor decomposition and liberation of reactive species. [29]

- **Facilitating Nanoparticle Growth**

The deposition of further precursor gases onto the nucleation centers' surfaces causes them to keep expanding. The mechanisms through which this growth can take place include surface diffusion, coalescence, and aggregation. The growth process can be influenced by variables like temperature, gas composition, and reaction time.

- **Removing Precursor Gases**

Once the nanoparticles of the desired size and morphology are synthesized, the precursor gases are removed from the reaction chamber. This is accomplished by cutting off the gas flow and cooling the reactor.

- **Collection of Nanoparticles from the Substrate**

The synthesized nanoparticles tend to stick and remain attached to the substrate surface after the precursor gases are removed. They can be harvested from the substrate and further characterized to be used in various applications.

These actions describe the whole procedure of Chemical Vapour Deposition (CVD) for the creation of nanoparticles. To optimize the characteristics of the resultant nanoparticles, researchers can adjust certain parameters throughout each stage [30].

3.2.5. Pyrolysis

It involves the decomposition of precursor gases at high temperatures in the absence of oxygen. This allows for the production of nanoparticles with controlled size and morphology.

In this process, a precursor material is dispersed in a suitable solvent or carrier gas which is then heated to the point when the precursor material starts decomposing, resulting in the formation of reactive species. These reactive species nucleate further and grow into nanoparticles.

Researchers can control the parameters to achieve nanoparticles of the desired shape and composition. These parameters are:

- Choice of Precursor Material
- Reaction Temperature
- Heating Rate
- Reaction Time
- Presence of A Catalyst

Pyrolysis offers several advantages over conventional methods for synthesizing nanoparticles, including scalability, greater versatility in precursor selection, and the ability to produce nanoparticles in various forms such as colloidal suspensions or powders [31].

However, it also has several challenges related to obtaining nanoparticles of uniform size or particle size distribution. Therefore, researchers should carefully outweigh the pros against the cons before employing it in nanoparticle synthesis.

3.2.6. Spinning

The spinning method involves nanoparticle synthesis through the rapid solidification of a liquid precursor by employing centrifugal force. This method is commonly used to produce metal and metal oxide nanoparticles.

In this method, a precursor suspension or solution is mounted on a rapidly rotating disc, and as the disc rotates, the centrifugal force induces a thinning effect on the liquid precursor. The rapid evaporation of solvent from the precursor results in the synthesis of nanoparticles.

The parameters that can influence the nanoparticle size, morphology, or composition include:

- Choice of Precursor Solution
- Spinning Speed
- Spinning Duration

The spinning method is primarily preferred because it is simple, scalable, and has the ability to produce nanoparticles with uniform size distribution and high surface area. It can be used to synthesize nanoparticles of metals, metal oxides, and hybrid materials. Spinning is often utilized to synthesize magnesium hydroxide nanoparticles in a spinning disk reactor and then use them as precursors for preparing magnesium oxide [32].

Although spinning offers numerous benefits, it also comes with its fair share of challenges, including unwanted nanoparticle agglomeration and difficulty in achieving precise control over nanoparticle size or shape. Researchers should carefully consider the advantages and disadvantages of this method prior to employing it in nanoparticle synthesis.

4. Conclusion

The studies showed that the nanoparticles, with small size and large surface area have a great ability to deliver the drug with more bioavailability as compared to the conventional dosage forms. Still there are compatibility issues with drug or with human body, but studies are ongoing to overcome these issues. Targeted drug delivery using nanotechnology is more effective against the disease with least side effects. No doubt, the nanotechnology has revolutionized the drug delivery system has opened new gates of research and development.

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