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Review On Nanoparticles, Its Synthesis And Applications In Drug Delivery & Cancer Therapy

[1]Sonam Upadhyay, [2]Rashmi Haldkar, [3]Reetesh Malvi, [4]Tarannum Fatima*

[1]Assistant Professor, [2]Associate Professor, [3]Associate Professor, [4]Research Scholar
[1]Jai Narain College of Pharmacy, Bhopal, Madhya Pradesh, India
[2]Sir Aatma Ram Institute of Pharmacy and Technology, Jabalpur, India
[3]Lakshmi Narain College of Pharmacy, Kalchuri, Nagar Raisen Road, Bhopal, Madhya Pradesh, India
[4]SMT Tarawati Institute of Biomedical and Allied Sciences, Roorkee, 247667, India

Abstract: The Nanotechnology is the manipulation of materials on a molecular or atomic scale, and it has the potential to revolutionize the pharmaceutical industry. By using nanotechnology, drug molecules can be made more stable, targeted to specific cells, and delivered in a controlled manner. This can lead to more effective treatments with fewer side effects. Examples of nanotechnology in modern pharmaceuticals include nanoparticle drug delivery systems, which can target cancer cells more effectively, and liposomal drugs, which can help drugs reach the desired location in the body. Additionally, following current advancements in the field includes the use of peptide-based nanoparticles for targeted drug delivery, and the use of gold nanoparticles for diagnostic imaging.

Index Terms **– Nanotech, Nanoparticle, Drug delivery, Diagnostics, cancer cells.**

1. Introduction

The 1950s are when the idea of nanotechnology first emerged, There's Plenty of Room at the Bottom, a talk by physicist Richard Feynman, in which he suggested the concept of manipulating individual atoms and molecules to produce new materials and devices. However, it wasn't until the 1980s, K. Eric Drexler, a physicist, first used the term "nanotechnology" in his book "Engines of Creation: The Coming Era of Nanotechnology".

In 1990s, advances in technology such as the atomic force microscope and the scanning tunnelling microscope allowed researchers to begin manipulating individual atoms and molecules, and research in the field of nanotechnology began to accelerate. In 2000, the National Nanotechnology Initiative was established in the US to coordinate and fund nanotechnology research across multiple government agencies.
Today, nanotechnology is an interdisciplinary field that involves scientists and engineers from many different backgrounds, including physics, chemistry, materials science, and biology. It has uses in many different fields, such as energy, electronics, medicine, devices and more. It involves the use of various tools and methods, such as electron microscopy, scanning probe microscopy, and lithography, to control and manipulate the properties of materials at the nanoscale. In medicine, for example, it can be used to create targeted drug delivery systems, diagnostic tools, and new materials for medical implants [1]

2. Nanotechnology in field of healthcare

The integration of nanotechnology into the healthcare sector promises to bring about significant developments and advancements in medicine. Nanotechnology has the potential to revolutionize medicine and healthcare by enabling the development of new diagnostic tools, therapies, and materials for medical implants. One of the most promising areas of nanotechnology in medicine is drug delivery. By using nanoparticles, drugs can be targeted to specific cells or tissues, and delivered in a controlled manner. This can lead to more effective treatments with fewer side effects. Examples of nanoparticle drug delivery systems include liposomes, which can be used to deliver cancer drugs to tumour cells, and dendrimers, which can be utilised to send DNA for

gene therapy. Nanotechnology is also being used to develop new diagnostic tools, such as biosensors and lab-on-a-chip devices. These tools can detect diseases at an early stage, enabling earlier treatment and better outcomes [2].

Also, nanoparticles are widely used in cosmetics and sunscreen as antioxidant and antireflectants. Nanoparticles have been widely used in commercial products other than cosmetics, such as personal care and paints. The white pigment titanium oxide nanoparticles (NPs) larger than 100 nm is widely used in cosmetic lotions and sunscreens. Similar to how AgNPs are utilised in a variety of products, including toothpaste, shampoos, wet wipes, food storage containers, and air sanitising sprays. The effectiveness of various NPs as additions in personal care products is being studied. Despite the growing popularity of items containing various nanomaterials, little is known about the dangers these materials pose to humans. Numerous investigations revealed that AgNPs were more harmful to human and animal cells than asbestos in terms of size, shape, and dosage dependence. Other NPs found in consumer products are also being studied to determine their potential dangers.

In addition, new materials for medical implants including prosthetic joints and heart valves are being developed using nanotechnology. These materials can be stronger, more biocompatible, and longer-lasting than traditional materials. The use of nanotechnology in regenerative medicine and tissue engineering is an emerging field. It can be utilised to make controlled release systems for medications and growth factors as well as scaffolds for tissue regeneration. Overall, Nanotechnology in medicine and healthcare has the potential to improve the diagnosis and treatment of diseases, reduce the cost and side effects of drugs, and improve the quality of life for patients [3].

2.2 Nanoparticles

Nanoparticles are particles that have at least one dimension measuring less than 100 nm. They can be made of various materials such as metals, polymers, lipids, or ceramics. Due to their small size, nanoparticles possess special qualities that set them apart from bulk materials.

In the field of pharmacy, nanoparticles can be classified based on their potential applications and the characteristics that make them appropriate for such uses:

1. **Drug delivery nanoparticles:** Drugs can be delivered directly to certain cells or tissues in the body using these nanoparticles. They can be made from a variety of materials, such as lipids, polymers, or metals, and can be engineered to have specific properties, such as targeting moieties, that enable them to selectively accumulate in specific areas of the body.

2. **Imaging nanoparticles:** These nanoparticles can be used to enhance the sensitivity and specificity of imaging methods like computed tomography (CT) scans or magnetic resonance imaging (MRI). They can be made from materials such as gold or iron oxide, and can be engineered to have specific properties that make them visible on imaging tests.

3. **Biomedical nanoparticles:** There are numerous biomedical applications for these nanoparticles, such as tissue engineering, wound healing, or gene therapy. They can be made from materials such as polymers, ceramics, or hydrogels, and can be engineered to have specific properties that make them suitable for these applications.

4. **Biocompatible nanoparticles:** These nanoparticles are designed to be non-toxic and compatible with living organisms, they can be used in different medical applications such as tissue engineering, drug delivery, imaging, etc.

5. **Theragnostic nanoparticles:** These nanoparticles are designed to have both diagnostic and therapeutic capabilities, for example, they can be used for imaging and drug delivery simultaneously.

Some examples of nanoparticles and their potential applications include:

- Gold nanoparticles, which can be used as contrast agents for diagnostic imaging and as catalysts in chemical reactions. They are a promising contender for breast cancer detection, targeted therapy, and cell imaging and tumour-specific medication delivery.

- Silver nanoparticles, Due to its antimicrobial capabilities, strong electrical conductivity, and distinctive optical features that may be used in a variety of applications.

- Quantum dots, semiconductor nanoparticles that may emit a variety of coloured light, and can be used as biosensors, labels for biological imaging, and in solar cells.

- Carbon nanoparticles, such as carbon nanotubes and graphene, which have high strength and conductivity, and can be used in electronics, energy storage, and biomedical applications.

- Liposomes, which are spherical, lipid-based nanoparticles that can be used to deliver drugs, vaccines, and genetic material.

- Dendrimers, which are highly branched, highly monodisperse nanoparticles that can be used as scaffolds for drug delivery and in biosensing [4-12].

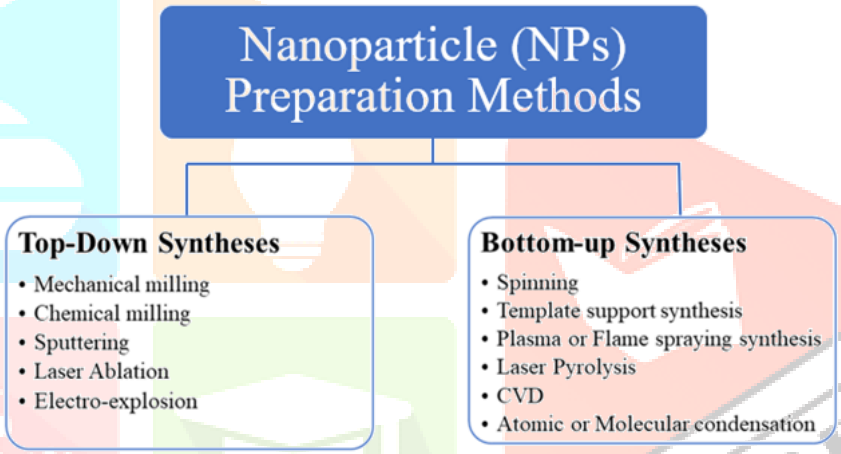

Fig. 1: Method of Preparation of Nanoparticles

2.2.1 Classification on based their origin

Based on their source, nanoparticles can also be categorised as either natural or artificial.

1. In nature, either by biological species or via human activity, natural nanomaterials are created. Natural resources can easily be used to create artificial surfaces with unique micro- and nanoscale templates and features for technological applications. Regardless of human activity, naturally occurring NMs are prevalent across the spheres of the Earth (i.e., in the aquatic environment, atmosphere, lithosphere, as well as in the biosphere). The NMs that make up Earth's spheres include the hydrosphere, which is made up of oceans, lakes, rivers, groundwater, and hydrothermal vents, the lithosphere, which is made up of rocks, soils, magma, or lava at specific stages of evolution, and the biosphere, which includes lower organisms like microbes and higher organisms like humans.

2. Synthetic (designed) nanomaterials can be created by physical, chemical, biological, or hybrid means as well as through mechanical grinding, engine exhaust, and smoke. The use of engineered NMs in consumer goods and industrial applications, as well as their growing manufacturing and subsequent release, has raised the issue of risk assessment methodologies recently. These risk assessment techniques are quite useful for predicting how modified NMs would behave and fare in diverse environmental media. The main problem with designed NMs is determining if current information is sufficient to predict their behaviour or if they behave differently from wild NMs in relation to their surroundings. Engineered NMs are now produced using several sources connected to possible uses [13-17].

2.2.2 Synthesis of Nanoparticles

A range of techniques, including physical, chemical, and biological ones, can be used to create nanoparticles. Ball milling, spray pyrolysis, and physical vapour deposition are examples of physical processes. Chemical methods include sol-gel, precipitation, and microemulsion. Biological methods include bacterial and fungal fermentation. The technique of choosing is determined by the planned application and the required attributes of the nanoparticles. But these methods are mainly classified under two classes: (a) Bottom-up synthesis and (b) Top-down synthesis.

Top-down synthesis:
Top-down synthesis of nanoparticles refers to the methods of reducing the size of larger particles to the nanoscale. Some common methods of top-down synthesis include:

- Mechanical grinding or milling: This involves using a mechanical force to break down larger particles into smaller ones. This can be done using equipment such as ball mills or planetary mills.
- Laser ablation: This involves using a high-energy laser beam to vaporize or ablate a larger particle, resulting in smaller nanoparticles.
- Electron beam irradiation: This involves using a beam of high-energy electrons to break down larger particles into smaller ones.
- High pressure homogenization: In this technique, a liquid is forced through a small hole by a high-pressure pump, forming tiny droplets that can later solidify into nanoparticles.
- Sonication: It is a process of using high frequency sound waves to break down larger particles into smaller ones.

These methods are useful in producing nanoparticles with specific properties and can be used in various applications such as catalysts, drug delivery, and electronics

Bottom-up synthesis:
Bottom-up synthesis of nanoparticles refers to methods that involve building up nanoscale particles from smaller building blocks, where nanoparticles are synthesized by assembling atoms or molecules in a controlled manner. This approach can be used to produce nanoparticles of variety of materials, and it is relatively easy to customise the structural shape and size of the NPs. However, it can be expensive and time-consuming. Some common methods of bottom-up synthesis include:

- Chemical vapor deposition (CVD): High-quality, high-performance solid materials are produced using the deposition technique known as chemical vapour deposition (CVD), often under vacuum. To create non-volatile solid thin films on substrates, a chemical interaction between an organometallic or halide compound that has to be coated and the other gases is known as CVD.
- Molecular beam epitaxy (MBE): This method involves depositing atoms or molecules onto a substrate in a controlled manner, resulting in the growth of single crystal nanoparticles.
- Sol-gel: This method involves the hydrolysis and condensation of a precursor solution to form a gel, which is then calcined to form nanoparticles.
- Self-assembly: This method involves the spontaneous organization of molecules into ordered structures, resulting in the formation of nanoparticles.

Biological methods, such as cell-mediated biosynthesis, are used to produce nanoparticles by using living organisms or cells (Bacteria, yeast, fungi, algae, plants etc). This method may be applied to create nanoparticles made of a variety of materials, and it is relatively easy to customise the structural shape and size of the nanoparticles. However, it can be expensive and time-consuming [18-23].

3. Nanoparticles in Drug delivery

Nanotechnology has evolved as a promising technology for drug delivery, offering multiple advantages such as improved bioavailability, increased resistance time in the body, precise targeting, increased safety, and reduced side effects. Nanoparticles are particularly well-suited for precision medicine therapies, as they can interact with biological systems, are chemically and geometrically tunable, and have a high surface-area-to-volume ratio. Nanoparticles can be used to improve the solubility of drugs, reducing the need for multiple doses and increasing the effectiveness of the drug. Nanoparticles can also be used to target specific areas of the body, meaning that more of the drug is delivered to its intended location. This makes the drug more effective and reduces side effects. Nanoparticles can also be used to deliver drugs to areas of the body that are otherwise difficult to target, such as the brain. This is because the Nanoparticles can cross the blood-brain barrier, which is something that many drugs cannot do. Nanoparticles can also be used to reduce the toxicity of drugs, as they can be attached to drugs to reduce their toxicity.

Furthermore, Nanoparticles have been used to deliver both small molecules and large biologics, such as DNA and proteins. This allows for the delivery of multiple drugs at once, which can be particularly beneficial in the treatment of chronic diseases. One of the key benefits of using nanoparticles in drug delivery is their ability to target specific cells or tissues. By attaching targeting moieties such as antibodies or peptides to the surface of nanoparticles, they can be directed to specific cells or tissues in the body, such as cancer cells. This allows for targeted delivery of drugs, which can improve the efficacy of treatment while reducing the dosage required, leading to fewer side effects.

Lipid and polymer-based nanoparticles are two of the most commonly used materials in drug delivery systems. Both types of nanoparticles have unique properties that make them suitable for different applications.

Lipid-based nanoparticles, such as liposomes, are composed of a phospholipid bilayer that can encapsulate drugs. They can be designed to target specific cells or tissues, such as cancer cells, and can be used to deliver drugs to these cells in a controlled manner. Liposomes have been used in the delivery of anticancer drugs, vaccines, and genetic material. They are biocompatible and non-toxic, making them a safe and effective option for drug delivery.

Polymer-based nanoparticles, such as polymeric nanoparticles, are composed of a variety of polymers. They can be engineered to have a prolonged release profile, and can target specific cells or tissues. Polymeric nanoparticles have been used in the delivery of a wide range of drugs, including anticancer drugs, proteins, and genes. They are biocompatible and can be easily synthesized, making them a versatile option for drug delivery.

Both lipid and polymer-based nanoparticles have their own advantages and disadvantages, depending on the specific application. Lipid-based nanoparticles are biocompatible and non-toxic, but they can be more difficult to synthesize and may have a shorter shelf-life than polymer-based nanoparticles. Polymer-based nanoparticles are versatile and easily synthesized, but they may not be as biocompatible as lipid-based nanoparticles [24-32].

Challenges of using nanoparticles in drug delivery:

One of the main challenges of using nanoparticles in drug delivery is the potential toxicity of nanoparticles. The small size of nanoparticles means that they can easily enter cells and tissues, which can lead to toxicity. In addition, the surface of nanoparticles can be functionalized with various molecules, such as targeting moieties, that can also lead to toxicity. Another challenge of using nanoparticles in drug delivery is the lack of appropriate regulations for their use in the healthcare industry. Further research is needed to fully understand the safety and efficacy of nanoparticles in drug delivery, and to develop appropriate regulations for their use in the healthcare industry [33-35].

Nanoparticles in treatment of cancer

Nanoparticles are being researched as a potential treatment for cancer due to their small size and ability to target specific cells in the body. For effective cancer therapy, it is essential to develop or engineer a drug or gene delivery system that has an excellent ability to target tumour cells sparing the normal healthy cells. It enhances therapeutic efficacy, thereby shielding normal cells from the effect of cytotoxicity. It can be

achieved by the well-organized delivery of NPs into the tumour microenvironment (TME), indirectly targeting cancer cells. These nano formulations should pass through numerous physiological and biological barriers. These barriers are complex systems of several layers (epithelium, endothelium, and cellular membranes) and components (mechanical and physicochemical barriers and enzymatic barriers).

These nanocarriers typically should possess certain fundamental characteristics such as

1) ability to remain stable in the vascular system (blood) until they reach their target, TME,
2) to escape the reticuloendothelial system (RES) clearance,
3) escape mononuclear phagocyte system (MPS),
4) accumulate in TME via tumor vasculature,
5) high-pressure penetration into the tumor fluid, and
6) reach the target and only interact with tumor cells.

Examples of some nano formulations used in Cancer treatment:

Abraxane is a nanoparticle-based chemotherapy drug used in the treatment of non-small cell lung cancer and breast cancer (NSCLC). It is a brand name for paclitaxel protein-bound particles for injectable suspension. The active ingredient, paclitaxel, is a chemotherapy drug that works by preventing the growth and division of cancer cells. In a mouse model study conducted at Rice University and the University of Texas MD Anderson Cancer Centre, nanoparticles were employed to deliver the medicine with increased effectiveness for treating head and neck cancer. The disclosed therapy makes use of Cremophor EL, which enables intravenous delivery of the hydrophobic paclitaxel. As a result of the poisonous Cremophor's side effects being reduced and the drug's targeting being significantly enhanced, a lower dose of the dangerous paclitaxel is required.

What makes Abraxane different from other paclitaxel formulations is that it is a nanoparticle-based drug delivery system. Instead of being dissolved in a solvent such as Cremophor EL, paclitaxel is bound to albumin, a protein found in human blood, to form nanoparticles. These nanoparticles are roughly 130 nm in diameter. This drug delivery method has several advantages over traditional paclitaxel formulations. Because Abraxane is a nanoparticle, it is less likely to cause hypersensitivity reactions, which are common with Cremophor-based paclitaxel. Abraxane also has a longer circulation time in the body than traditional paclitaxel, which can help to target more cancer cells. Additionally, Abraxane is associated with less peripheral neuropathy (nerve damage) than traditional paclitaxel.

Genexol PM is an innovative nano formulation of paclitaxel and sterile lyophilized polymeric micellar formulation without CrEL. Genexol PM, according to trials, was found to have a three-times higher maximum tolerated dose (MTD) in nude mice. Besides, the biodistribution exhibited two- to three-times higher levels in different tissues such as liver, spleen, kidney, and lung and more prominently in cancer cells. It has been approved in South Korea to treat metastatic breast cancer (MBC).

Doxorubicin (also known as Adriamycin) is a chemotherapy drug that is used to treat a wide range of cancers, including breast, ovarian, lung, and bladder cancer. It belongs to a class of drugs called anthracyclines, which work by inhibiting DNA synthesis and causing damage to the genetic material of cancer cells, leading to their death. Doxorubicin was administered to breast cancer cells via a nanoparticle chain in mouse research at Case Western Reserve University. The researchers chemically connected one doxorubicin-loaded liposome to three magnetic, iron-oxide nanospheres to create a chain of nanoparticles that was 100 nm long. After the nano chains had entered the tumour, magnetic nanoparticles were made to vibrate by creating a radiofrequency field. This caused the liposome to break, releasing the medication in its free form, which was then dispersed throughout the tumour. Nanotechnology was more effective at stopping tumour growth than the traditional doxorubicin treatment, and it caused less harm to healthy cells because far lower dosages of doxorubicin were utilised. The most common side effects of doxorubicin include nausea, vomiting, hair loss, mouth sore, and fatigue.

Hydrogels are a class of materials that can be used in the treatment of breast cancer. Hydrogels are made up of water and polymer, and they can be formed into a wide range of shapes and sizes. They are similar to the natural extracellular matrix and can mimic the mechanical and biochemical properties of the microenvironment, which can help to study the behaviour of cancer cells and design new therapeutic strategies. One of the main applications of hydrogels in breast cancer treatment is as a scaffold for tissue engineering. Hydrogels can be used to create three-dimensional structures that mimic the structure and

function of breast tissue. These structures can be used to support the growth of normal breast cells, which can be used to repair or replace tissue damaged by cancer [36-37].

Advantages of Nanoparticles in Cancer therapy:

The utilization of nanotechnology in the diagnosis, treatment, and management of cancer has led to a whole new era. NPs, either by active or passive targeting, augment the intracellular concentration of drugs while avoiding toxicity in the healthy tissue. The targeted NPs can be designed and altered as either pH-sensitive or temperature-sensitive to establish and regulate the drug release. The pH-sensitive drug delivery system can deliver drugs within the acidic TME. Similarly, the temperature-sensitive NPs release the drugs in the target site due to changes in temperature brought in by sources like magnetic fields and ultrasound waves. In addition, the "physicochemical characteristics" of NPs, such as shape, size, molecular mass, and surface chemistry, have a significant part in the targeted drug delivery system. Further, NPs can be modified according to the target and used to target a particular moiety.

Conventional chemotherapy and radiation therapy have several disadvantages concerning efficacy and side effects because of uneven dispersal and cytotoxicity. Therefore, cautious dosing is required that effectively kills cancer cells without any significant toxicity. To reach the target site, the drug has to pass several fortifications. Drug metabolism is a very complex process. In physiological conditions, the drug needs to pass TME, RES, BBB, and kidney infiltration. RES or macrophage system is made up of "blood monocytes, macrophages, and other immune cells". MPS in the liver, spleen, or lungs react with the drugs and activate "macrophages or leukocytes" that rapidly remove the drug. This leads to a short half-life of the drug. To overcome this, NPs with "surface modification," such as PEG, bypass this mechanism and increase the "drug half-life." Besides, kidney infiltration is a crucial function in the human body. Proper kidney infiltration thus minimizes the toxicity caused by NPs.

The brain-blood barrier (BBB) is a specialized protection structure offered to protect the CNS from harmful and toxic agents. "Brain capillary endothelial cells" are arranged in the form of a wall that provides essential nutrients to the brain. Since the primary function of BBB is to block toxic agents to reach the brain, currently available chemotherapy agents for brain cancer are highly limited to intraventricular or intracerebral infusions. However, NPs are known to cross BBB. Now, several approaches such as EPR effect, focused ultrasound, peptide-modified endocytosis, and transcytosis are used to deliver NPs. Glutathione PEGylated liposome encapsulated with methotrexate showed improved methotrexate uptake in rats. Au-NPs are often used as they have proven to help transport drugs to induce apoptosis.

NPs being carriers also increase the drug stability by preventing the degradation of the encapsulated cargo. Additionally, a large volume of drugs can be encapsulated without any chemical reaction. Dry solid dosage forms are more stable than nano liquid products. Stabilizers can be used to enhance stability. Yet another way to increase stability is to use porous NPs.

NPs can be administered through several routes like oral, nasal, parenteral, intra-ocular etc. NPs have a high surface-to-volume ratio and intracellular uptake. Studies have reported that NPs are more effective than microparticles as drug carriers [38-43].

Conclusion:

Through the delivery of tiny molecules for cancer detection, diagnosis, and therapy, nanotechnology has demonstrated a promising new era in cancer treatment. In the therapeutic context of several cancer types, cancer therapies based on the unique qualities of NPs are being widely employed. When compared to traditional medications, NP-based DDS is associated with improved pharmacokinetics, biocompatibility, tumour targeting, and stability. Additionally, NPs offer a great platform for combination therapy, which aids in the recovery from MDR. Numerous NP forms, including metallic, hybrid, and polymeric NPs, have demonstrated increased drug delivery efficacy as a result of increased study.

This is an emerging area, and it is anticipated that with growth in proteomics research on the "mechanism of cancer origin, MDR, occurrence," more NP-based drugs can be exploited. Compared to the mammoth amount of investigations, only a few NP-based drugs are actually in use, a few others in clinical trials, and most in the exploratory stage. For rational nanotechnology design, more efforts must be reserved in "understanding toxicity, cellular and physiological factors that regulate NP-based drug delivery, EPR, and PC mechanism" in

the human body. Based on the evidence cited above, we presuppose that the revolution in clinical translation for NP-based cancer therapy will be attained with nanotechnology and cancer therapy development.

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