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Nanoparticles: Current Approaches and Challenges on Cancer Treatment

Qhamarunnisa[1], Treeza Linet Crasta[1], Subhashitha S*[1] Ravi Kumar Naik[2]
*[1]*Correspondence author, Karavali College of Pharmacy, Mangalore*
[1]*UG Scholar, Karavali College of Pharmacy, Mangalore.*
[2]*Principal, Karavali College of Pharmacy, Mangalore.*

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ABSTRACT
According to the International Union of Pure and Applied Chemistry, nanoparticles (NPs) are tiny particles whose dimensions range from 1 to 100 nanometer. Therapeutic agents can be loaded into these particles by dissolving them within the polymer, trapping them inside, encapsulating them, or fastening them to the particle's surface. The choice of manufacturing method must match the chemical and physical traits of both the polymer and the drug, while the technique itself shapes the particle's internal architecture, drug release behaviour in vitro, and ultimate biological destiny. In cancer treatment, directing chemotherapeutic agents with specially designed nanoparticles addresses many shortcomings of traditional chemotherapy: passive or active targeting can raise drug or gene levels inside tumor cells while sparing healthy tissue. Overall, nanotechnology is opening a new chapter in oncology by enabling precise delivery of small molecules for cancer detection, diagnosis and therapy.

KEYWORDS: Drug delivery, nanoparticles, polymer, chemotherapy, nanotechnology, carrier.

I. INTRODUCTION

International Union of Pure and Applied Chemistry defines nanoparticles (NPs) as microscopic particles with 1-100 nm in dimension.[1] The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed.[2] Nanoparticle usually forms the core of nano-biomaterial .It can be used as the convenient surface for molecular assembly, and may be composed of inorganic or polymeric materials.

Rationale behind the development and use of nanoparticles:

The important technological advantages of nanoparticles used as drug carriers are high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral application and inhalation. Nanoparticles can also be designed to allow controlled (sustained) drug release from the matrix. These properties of nanoparticles enable improvement of drug bioavailability and reduction of the dosing frequency, and may resolve the problem of nonadherence to prescribed therapy, which is one of the major obstacles in the control of various epidemics.

1. To decrease the toxicity & occurrence of adverse reactions.
2. Better drug utilization.
3. Controlling the rate and site of drug release.
4. Provide a more predictable drug delivery system.
5. Providing a greater convenience or better patient compliance.
6. The therapeutic effectiveness of the drug (.e, the overall pharmacological response) per unit dose is enhanced.
7. They are reproducible.
8. They can be freeze dried so obtained in dry powder form.
9. Non-toxic and biodegradable.
10. Relatively cheaper & stable.

Characteristics of nanoparticles

The most efficient way for a nanoparticle to systematically deliver a Drug is by remaining in the blood circulation for an extended time Period to the target cells and for the constitutive delivery of a drug to the target site.[3]

Particle size and shape of nanoparticles

Particle size and size distribution are the most important characteristics of nanoparticle

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systems. They determine the in vivo distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles.[4] Nanoparticle size is often manipulated to be big enough to avoid any invasion into blood capillaries and also small enough to escape from macrophages of the reticuloendothelial system and to Prevent the elimination of the nanoparticle from the system.[5]

In addition to size, the shape of NPs has newly been identified as an important factor that plays a critical role in circulation time, biodistribution, cellular uptake, as well as targeting in cancer drug delivery. The majority of nanocarriers are generated in spherical form, which is mostly developed for anticancer drugs, whereas viruses and bacterial nanocarriers are found in various shapes such as filaments or cylinders.[6]

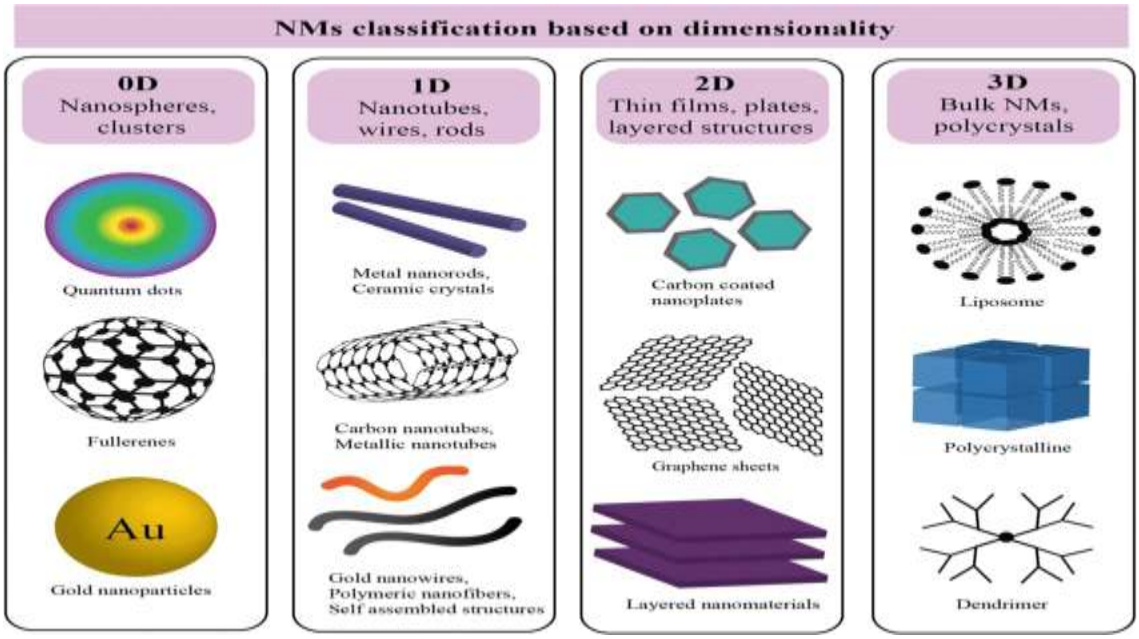

Figure 1: NMs classification based on dimensionality

Charge of nanoparticles

The charge on polymeric nanomaterials is a result of functional groups incorporated during polymerization. Cationic polymers result from the incorporation of amine containing monomers, while anionic polymers typically result from acid containing monomers.[7, 8]

Particle surface characteristics

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation.[9] Apart from the size of nanoparticles; their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (Opsonins). This in turn influences the in vivo fate of nanoparticles.[10, 11] Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes.[12] The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles.[13]

Nps as drug delivery systems in cancer medicine

Recently, NPs have been taken into consideration as drug carriers. Nanocarriers change the pharmacokinetic properties of drugs to improve their efficiency and decrease their side effects. In the structure of NPs used for drug delivery, various kinds of materials are used, such as polymers, metal particles, lipids, and so forth. According to the structure of NPs, different shapes and sizes of them can be produced. Drug delivery systems (DDS), which are dependent on nanocarriers, have entered into the world pharmaceutical market. Their application in DDS is increasing every day.[1]

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TYPES OF NANOCARRIERS

LIPOSOMES

Liposomes are supramolecular aggregates formed by amphiphilic components, such as polar lipids, dispersed in an aqueous solution. These building blocks form bilayer structures organized in closed, spherical vesicles. Liposomes have an aqueous core and therefore possess core-shell structures that enable the encapsulation of both hydrophilic and hydrophobic molecules.[14] Liposome can also be loaded with nanoparticles (NPs) of various nature and size, thus extending the field of application of this class of materials with extraordinary characteristics and properties that have dominated the last decades of research.[15]

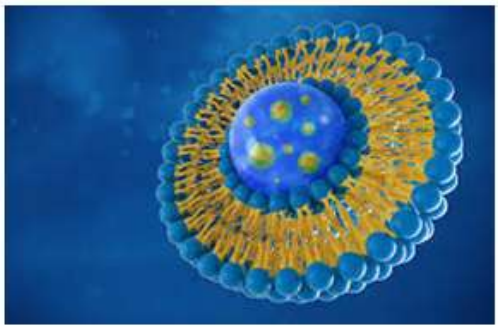

Figure 2: structure of liposome

DENDRIMERS

Dendrimers consist of globular molecules made out of branched layers (generations). Such a precise synthesis leads to obtaining monodisperse molecules. On their outer surface, dendrimers can be engineered to have various functional groups such as COOH, COONa, NH2, or OH.[16] Therefore, after very simple surface modification, dendrimers render intelligent nanoparticles, transporting drugs into specific areas and at the same time can be used for monitoring the state of organs attacked by cancer cells, as well as the progress of the curing process. They can help to limit the anti-cancer drug delivery to designed goals only, eliminating many side effects of chemotherapy.[17]

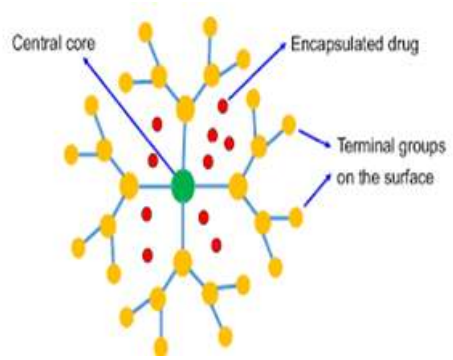

Figure 3: structure of dendrimers

POLYMERIC MICELLES

Polymeric micelles are self-assembled, nano-sized (5–100 nm), colloidal particles consisting of amphiphilic copolymers which form spontaneously in an aqueous environment. Above the so-called 'critical micelle concentration' (CMC), the single chains of polymers associate to minimize the contact of the hydrophobic segment with the aqueous media, leading to the formation of a core-shell micellar structure.[18] Each part of a polymeric micelle plays a different role in drug delivery. The outer shell surface modification.[19] The corona is responsible for interactions with biocomponents in the blood circulation (such as proteins) and the cell membrane. The shell provides stealth properties that render the micelles less prone to phagocytosis by the reticuloendothelial system (RES), resulting in prolonged blood circulation, a higher chance of EPR-mediated (Enhanced Permeability and retention) drug delivery and subsequently enhanced drug efficiency.[18]

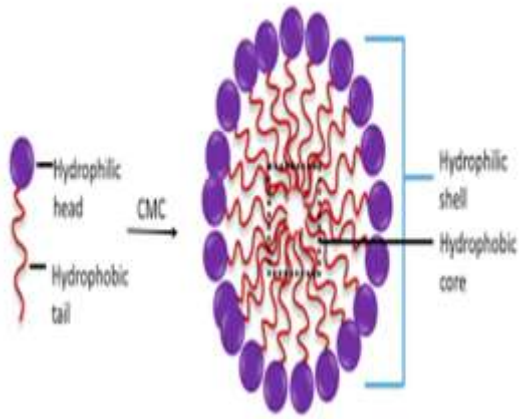

Figure 4: structure of polymeric micelles

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MAGNETIC NANOPARTICLES

Carbon magnetic nanoparticles (CMNP) are made up of spherical particles of 40-50 nm in diameter with iron oxide particles dispersed in a carbon-based host structure. [20] Iron oxide magnetic nanoparticles can also be sheathed with sugar molecules.[21] Therefore these are not recognized by the immune system. When these particles are brought under the influence of an external magnetic field, they heat up the tumor cells and destroy them without affecting the surrounding healthy tissues. [22] The magnetic nanoparticles can be targeted to specified tumor cells by adding nanoscale surface receptors (targeting moieties). These receptors specifically recognize the target tumor tissue and bind to it and release the drug molecules. Different tumor cells exhibit different cell receptors. Iron oxide nanoparticles can also be coated with amino groups to achieve cell specific delivery of therapeutic agents.[23]

Figure 5: structure of magnetic nanoparticles

GOLD NANO SHELLS

Gold nanoshells are used in cancer detection, treatment, and medical biosensing with the help of their attractive set of optical, chemical, and physical properties. [24]The conjugation of gold nanoshells with conventional therapies has reduced its side effect as the gold nanoshells provide enormous sensitivity, throughput, and flexibility to increase the quality life of patients. [25]

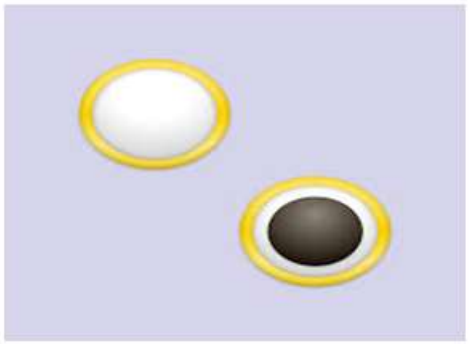

Figure 6: structure of goldnano shells

CARBON NANO TUBES

Carbon nanotubes are rolled-up like tubular structures composed of benzene rings lying under the fullerene structure family.[26] Carbon nanotubes based upon their nanometric dimensions have been categorized into two groups, i.e., single-walled nanotubes (SWNT) composed of one layer of cylinder graphene and multi-walled nanotubes (MWNT) consisting of multiple concentric graphene layers.[27]

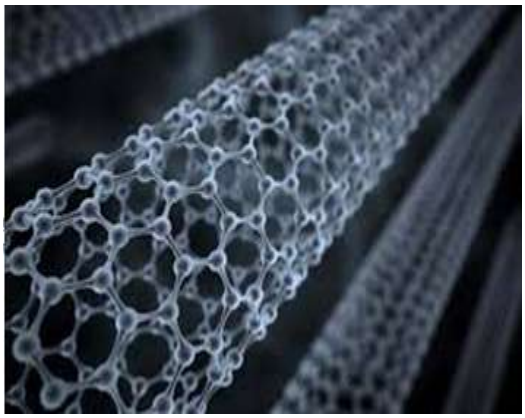

Figure 7: structure of carbon nano tubes

QUANTUM DOTS

Quantum dots with their distinctive photophysical properties, quantum dots (QDs) are frequently constructed from hundreds to thousands of atoms of group II and group VI molecules.[28] The tumor might be seen while the medicine is being released at the desired location using this nanoparticle. [29] Three components make up the majority of commercially available QDs: a core, a shell, and a capping substance. Materials used in semiconductors make up the core. Shells are constructed around the semiconductor core using ZnS. The two layer QDs are enclosed in a cap made of various materials[30]

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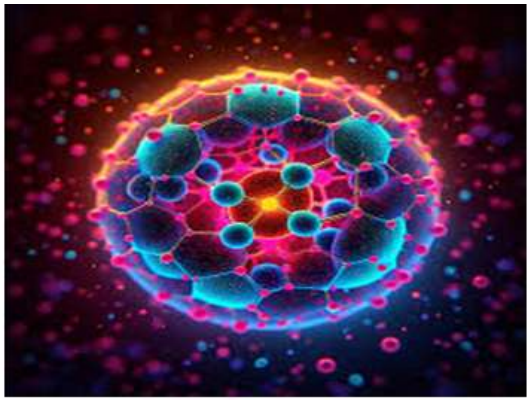

Figure 8: structure of quantum dots

TUMOR TARGETTING STRATEGIES

1) Passive targeting

Passive targeting of nanoparticles relies upon the unique pharmacokinetics of nanoparticles including minimal renal clearance and the "enhanced permeability and retention" (EPR) effect in the tumor. Angiogenesis and vascularization are well-characterized for tumors. [31] In tumors, blood vessel walls become leaky because of defective vascular architecture, including poorly aligned endothelial cells with wide fenestrations and a lack of a smooth muscle layer. These properties result from rapid angiogenesis or vascularization because tumor cells develop so fast and demand a large supply of nutrients and oxygen.[32] The vascular permeability of tumor tissues can also be enhanced by the actions of secreted factors such as kinin and vascular endothelial growth factor.[33,34] Furthermore, tumor tissues usually lack effective lymphatic drainage. Therefore, macromolecules or leukocytes can be drained through the leaky blood vessels and be retained. This phenomenon was defined as EPR effect.[35, 36] As a result of such increased vascular permeability, polymeric micelles, liposomes, and dendrimers ranging from 50 to 500 nm in size can be selectively delivered to tumor tissue.[37, 38] When these particles are loaded with anticancer drugs, the drugs could be selectively delivered to the tumor tissue. In contrast, very small nanoparticles (<20-30 nm in diameter) can easily pass through the leaky capillary wall in the tumor but can also be returned to circulating blood by diffusion. [39] Therefore, small particles have good permeability but poor retention. However, after conjugation with a targeting ligand, their retention in the tumor could be greatly enhanced.[40]

The EPR effect greatly relies on the fundamental tumor biology, such as

- The degree or extent of angiogenesis and lymph angiogenesis
- The extent or degree of perivascular tumor invasion
- Intratumor pressure.

These factors, combined with physicochemical characteristics of NPs, determine the efficiency of NP drug delivery system.[41]

2) Active targeting

Active targeting is able to significantly increase the quantity of drug delivered to the target cell compared to free drug or passively targeted nano systems. After accumulation in the tumor region, the drug efficiency can be even increased by the so-called active targeting. This is achieved through the decoration of the nanocarrier surfaces with ligands binding to receptors over expressed onto the tumor cells .This strategy will improve the affinities of the nanocarriers for the surface of cancer cell and thus enhance the drug penetration. The first evidence of this phenomenon was proposed in 1980 with antibodies grafted in the surface of liposomes,[42] followed by other various kinds of ligands like for instance peptides, nucleic acids, aptamers.[43,44] Active targeting depends on specific ligands or molecules, like transferrin and folate, which binds to molecules or receptors that are specifically expressed or over-expressed on the target cells (diseased organs, tissues, cells or sub-cellular domains).[45] This type of targeting is called ligand mediated targeting.[46]

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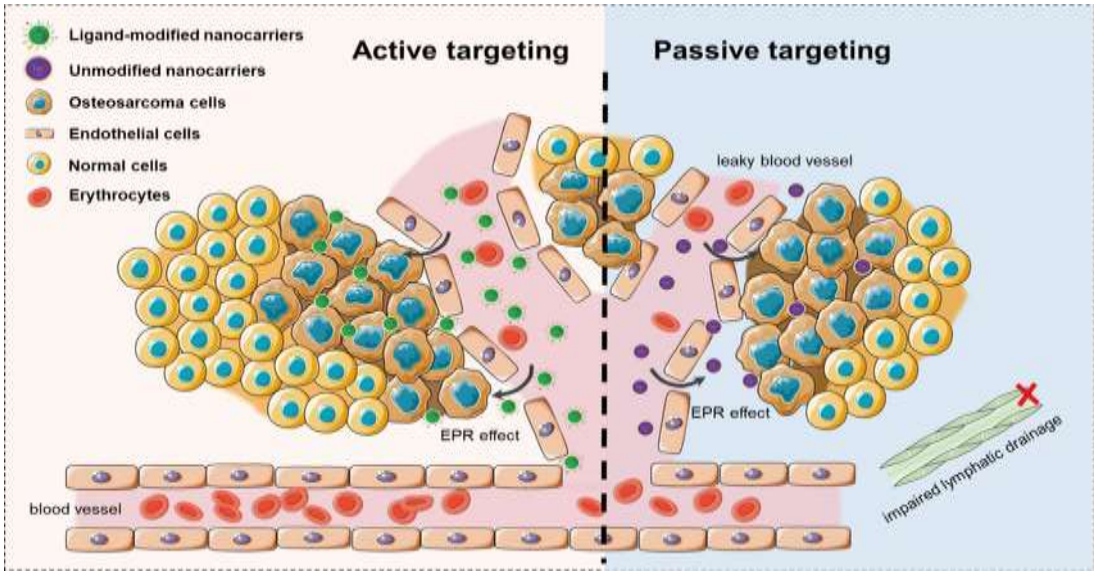

Figure 9: Active and passive targeting

Preparation techniques of nanoparticles: The selection of the appropriate method for the preparation of nanoparticles depends on the physicochemical characteristics of the polymer and drug to be loaded. On the contrary, the preparation techniques largely determine the inner structure, in vitro release profile and the biological fate of these polymeric delivery systems.

Two types of polymeric systems with different inner structures are apparently possible:-

- A matrix type system consisting of an entanglement of oligomer or polymer units (nanoparticles/nanospheres)
- A reservoir type of system comprised of an oily core surrounded by an embryonic polymeric shell (nanocapsules)

The drug can either be entrapped within the reservoir or the matrix or can be adsorbed on the surface of these particulate systems.

Methodologies:

1. Amphiphilic macromolecule cross-linking:
a) Heat cross-linking.
b) Chemical cross-linking.
2. Polymerization based methods:
a) Polymerization of monomers in-situ.
b) Emulsion (micellar) polymerization.
c) Dispersion polymerization.
d) Interfacial condensation polymerization.
e) Interfacial complexation.
3. Polymer precipitation methods:
a) Solvent extraction/evaporation.
b) Solvent displacement (nanoprecipitation).
c) Salting out.

ADVANTAGES OF NANOPARTICLES IN CANCER TREATMENT

Using targeted nanoparticles to deliver chemotherapeutic agents in cancer therapy offers many advantages to improve drug/gene delivery and to overcome many problems associated with conventional chemotherapy. For example, nanoparticles via either passive targeting or active targeting have been shown to enhance the intracellular concentration of drugs/genes in cancer cells while avoiding toxicity in normal cells. In addition, the targeted nanoparticles can also be designed as either pH-sensitive or temperature-sensitive carriers.

The pH-sensitive drug delivery system can deliver and release drugs within the more acidic microenvironment of the cancer cells and/or components within cancer cells. The temperature-sensitive system can carry and release drugs with changes in temperature locally in the tumor region provided by sources such as magnetic fields, ultrasound waves, and so on so that combined therapy such as chemotherapy and hyperthermia can be applied. The targeting of nanoparticles to tumors via cancer-specific features/moieties has also been shown to minimize the effects of composition, size, and molecular mass of nanoparticles on their efficacy. Targeted nanoparticles can be further modified or functionalized to reduce toxicity. For example, modifying nanoparticles surface chemistry could reduce their toxicity and immunotoxicity.

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DNA Nanotechnology for Cancer Therapy DNA-based nanostructures have been synthesized for DNA sensors to detect nucleic acid, DNA-coated gold NPs for lead sensing by hybridizing Pb-activated DNA zyme to the linking DNA, scaffolds to organize organics, inorganic, and biomolecules into distinct morphology molecular transporters, and drug delivery.[49]

Nanotechnology for Small Interfering RNA (siRNA) Delivery siRNAs are small ds RNA molecules (around 21 nucleotides long) that suppress the expression of genes in the target. This process is known as "RNA interference." A few siRNA-based NPs that are currently under clinical investigations are ALN-TTR01 that is used to target the transthyretin gene to treat transthyretin-mediated amyloidosis, and Atu027, which is a liposomal siRNA that targets protein kinase N3 and TKM-ApoB that knock downs the expression of ApoB.[50,51]

Nanoparticles in Immunotherapy The immune system sets an important part in the establishment and development of cancer cells. The advancement of immunotherapy has revolutionized cancer therapy. It is found that NPs not only help in target delivery of chemotherapy but can also be used in combination with immunotherapy. There are several approaches in immunotherapy aimed at activating the immune system against cancer cells[52] by "immune checkpoint blockade therapy," "cancer vaccine therapy," "chimeric antigen receptor (CAR)-T cell therapy," and "immune system modulator therapy".[53-55] NP-based immunotherapy includes "nanovaccines," "aAPCs (artificial antigen-presenting cells)," and "immunosuppressed TME targeting." Nanovaccines specialize in delivering "tumor-associated antigens" and "adjuvants" to antigen-presenting cells, such as dendritic cells (DCs).[56] Moreover, these can also be employed as adjuvants to enhance "APC antigen presentation" and promote DC maturation that leads to the stimulation of cytotoxic T cells that have anti-tumor function.[57,58] Liposome's, PLGA NPs, gold NPs are found to have the ability to deliver TAAs into DCs in the cytoplasm.[59] Mesoporous silica, the most used inorganic NP, has exhibited an adjuvant role, leading to immune response stimulation.[60] Artificial APCs interact with MHC-antigen complexes directly which binds to T cells. They also bind to co-stimulatory molecules that bind to co-stimulatory receptors leading to T cell activation.[61]Targeting the immune-suppressed TME is yet another method of using NPs in immunotherapies. This is done by targeting essential cell types in TME such as "tumor-associated macrophages (TAMs)," regulatory T cells, and "myeloid-derived sup pressor cells (MDSCs)." Besides, the combination of chemoimmunotherapy has been demonstrated to be a capable approach in cancer therapy. For instance, a study has shown that co-loading Nutlin-3a, which is a chemotherapeutic agent and cytokine GM-CSF, in "spermine-modified acetylated dextran (AcDEX) NPs" improved cytotoxic CD8 (+) T cells proliferation and activated an immune response.[62] "Programmed cell death protein 1 (PD-1)" and "programmed cell death ligand 1 (PD-L1)" are some of the essential immune checkpoints.[63] Hence immune checkpoint inhibitors are used to target these using NPs. According to a study, conventional immune check point inhibitors of PD-L1/PD-1 displayed inconsistent responses. To enhance the chances and bonding of immune checkpoint inhibitors and immune checkpoints, multivalent poly (amidoamine) dendrimers were used. Usage of these dendrimers not only showed enhanced PD-L1 blockade but also showed improved drug accumulation at the tumor site.[64]

Nanoparticles in Cryosurgery Cryosurgery is an advanced practice of freeze-destroying cancer tissue. Although this is less invasive and causes intraoperative bleeding and postoperative complications, certain drawbacks like inadequate freezing capacity and damage to adjacent cells need to be addressed. [65] The rise of nanotechnology has enabled the use of NPs in cryosurgery

Significant challenges in the clinical application of nanoparticles

At present, as nanotechnology has bloomed, the amount of knowledge and research put into nanoparticles has steeply raised. But only a few of them actually make it up to clinical trials. Most of them only halt at in vivo and in vitro stages. Each individual nano formulation has particular challenges in their clinical translation, but most NPs face similar challenges that can be divided into biological, technological, and study-design related. Biological challenges include lack of routes of administration, tempering biodistribution, the channel of NPs across the biological barriers, their degradation, and toxicity. [66] NPs are usually injected via intravenous injections directly into the blood, which takes away NPs, making it challenging to stay and interact with the target site. As a result, a high concentration drug is used, which might not provide desired therapeutic effects.[67]

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Controlling the biological fate of NPs is very hard and needs a lot of focus. Even though NPs are made up of biosafety materials and are modulated accordingly to increase the retention time and half-life, there runs a risk of lung, liver and kidney damage. Some factors that govern toxicity are surface area, particle size and shape, solubility, and agglomeration.[68] Technological challenges of NPs include scale-up synthesis, equal optimization, and performance predictions. These are very crucial in safeguarding the clinical success of NPs.[69] Study-design challenges like study size, intent, and timing of NP therapies during the therapy impact significantly during clinical studies. Most of the studies revolve around "cell and animal models" that may not provide comprehensible results in human trials. Therefore, the usage of a single model is tough to imitate natural reactions in the human body.[70]

Synthesis of NPs:

The NPs are of different shapes, sizes, and structures. To achieve this, numerous synthesis methods are adopted. These methods can be largely categorized into two major groups: 1) bottom-up approach and 2) top-down approach. These approaches can be further classified into different subclasses based on reaction conditions and operation (Fig. 10).

Bottom up Approach

This method involves building material from atoms to clusters to NPs, i.e., building from simpler substances, hence known as constructive method. Some commonly used methods are spinning, solgel synthesis, chemical vapor deposition (CVD), plasma or flame spraying synthesis, laser pyrolysis, and biosynthesis.

Top down Approach

It is also known as the destructive method, which reduces bulk material or substance to synthesize NPs. A larger molecule is broken down or decomposed into smaller units that are converted into NPs. It includes techniques such as mechanical milling, nanolithography, chemical etching, laser ablation, sputtering, electro explosion, and thermal decomposition. Remarkably, the morphological parameters such as size, shape and charge of NPs can be modified by changing the reaction conditions and other synthesis parameters. Besides, the growth mechanism also determines the chemical properties of NPs. Hence understanding the growth mechanism is essential to synthesize required NPs

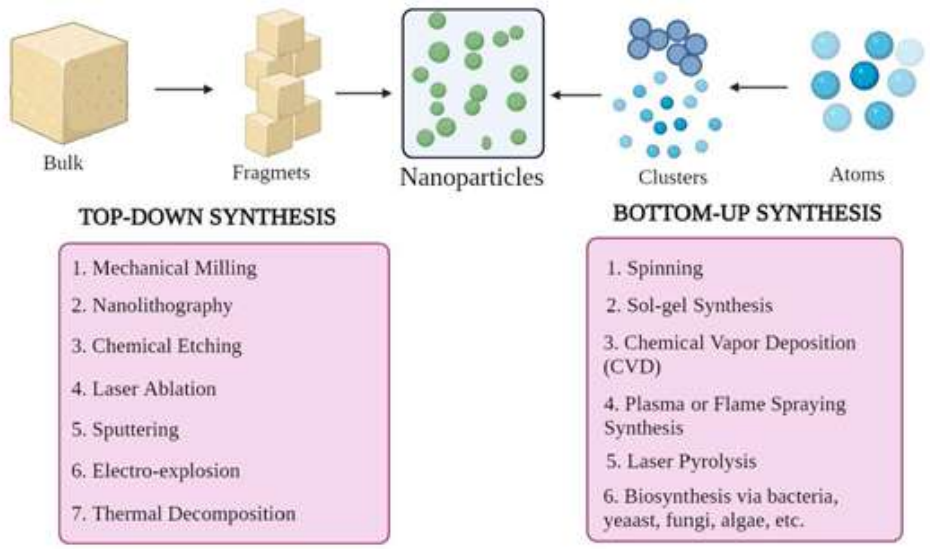

Figure 10: Classification of NP synthesis i. top-down and ii. Bottom up approaches

II. CONCLUSION AND FUTURE PROSPECTIVE

Nanotechnology has shown a promising new era of cancer treatment by delivering small molecules for cancer detection, diagnosis, and therapy. Cancer therapies based on the exceptional features of NPs are being vastly used in the clinical setting of several cancer types. NP-based DDS is linked with enhanced pharmacokinetics, biocompatibility, tumor targeting, and stability compared to conventional drugs. Nanoparticles

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offer a new method of tumor targeting, already available in clinical practice, which can concomitantly improve the efficacy and decrease the toxicity of existing or novel anticancer agents. In the near future, the use of nanotechnology could revolutionize not only oncology, but also the entire discipline of medicine.

The future perspectives of nanoparticles in cancer diagnosis and treatment are highly promising. Following are some potential areas where nanoparticles will have a significant impact:

Early cancer detection: NPs can be engineered to specifically target biomarkers associated with cancer cells, allowing for highly sensitive and specific early detection. This could enable the diagnosis of cancer at its earliest stage, when treatment is most effective.

Improved imaging techniques: NPs can enhance existing imaging modalities such as MRI, CT, and optical imaging. By functionalizing nanoparticles with targeting ligands and contrast agents, they can improve the resolution, sensitivity, and specificity of cancer imaging, enabling accurate tumor localization and monitoring of treatment response.

Targeted drug delivery: NPs can serve as vehicles for targeted drug delivery, improving efficacy and reducing the side effects of chemotherapy. They can encapsulate anticancer drugs and deliver them directly to tumor sites, minimizing damage to healthy tissues. Additionally, stimuli-responsive nanoparticles can release drugs in response to specific triggers, such as pH, temperature, or enzyme activity within the tumor microenvironment.

Combination therapy: NPs offer opportunities for combining multiple therapeutic modalities into a single system. For example, nanoparticles can be loaded with chemotherapy drugs, immunotherapeutic agents, or gene therapies, allowing for synergistic effects and personalized treatment approaches. This approach holds promise for overcoming drug resistance and improving overall treatment outcomes.

Theranostics: NPs can integrate both diagnostic and therapeutic functionalities into a single system, known as theranostic nanoparticles. These multifunctional nanoparticles can simultaneously diagnose cancer, deliver therapy, and monitor treatment response. They have the potential to revolutionize personalized medicine and enable real-time monitoring of treatment efficacy.

Immunotherapy enhancement: NPs can play a crucial role in enhancing the efficacy of immunotherapies, such as immune checkpoint inhibitors or cancer vaccines. They can be used to deliver immunomodulatory agents, antigens, or adjuvant directly to immune cells or tumor sites, stimulating a robust immune response against cancer cells.

Microenvironment modulation: NPs can be designed to target the tumor microenvironment and modify its characteristics. They can normalize abnormal blood vessels, enhance drug penetration into tumors, modulate immune responses, or inhibit metastasis, thus improving the overall treatment outcomes.

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