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Review Article

Nanocarrier Platforms in Cancer Therapeutics: Design, Advances and Clinical Translation Challenges

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Abstract

Nanotechnology has emerged as a transformative frontier for detecting and treating various types of tumours more accurately. As a leading technology, nanotechnology assists in overcoming the issues linked with traditional antitumor drug systems. Nanocarriers (NCs) are colloidal systems developed for precise drug delivery; their main objective is to surpass the protective and efficient barriers.

Nanocarriers have been widely studied over the last few decades as they are highly helpful and play an important role in drug delivery across different fields. They show better performance compared to other methods by overcoming the limitations related to low targeting ability, damage to healthy cells, toxicity, and immediate drug release.

To achieve this goal, novel NCs like microemulsions, vesicular (liposomes), and nanoparticular NCs are created and explored. These new NCs have unique improved penetration and retention in the tumour tissue. Nano-therapy has advanced the delivery of chemotherapeutic medicines in cancer. Additionally, their uses in many other therapeutic areas have been remarkable, and there is yet much more to be discovered to facilitate their successful clinical translation.

Keywords: Nanotechnology, Nanocarriers, Targeted therapy, Cancer therapeutics

Introduction:

Cancer is an increasingly prevalent disease that continues to be a serious health problem, significantly impacting people worldwide; thus, it becomes one of the major causes of mortality. With the continuous rise in cancer cases, research efforts are increasingly directed towards better treatment strategies and improved outcomes. [1]

The effectiveness of treatment varies with the disease's category, its region, and its level of growth, while improvement in cancer care depends on making treatments that are related to the genes and molecules, ensuring more effective and targeted outcomes. [1,2]

Nevertheless, traditional delivery methods, including chemotherapy, radiation therapy and surgical procedures, are considered a major approach in cancer treatment, which frequently fails to maintain consistent effectiveness due to certain drawbacks, such as generalised toxicity, low specificity, chemoresistance, limited permeability across biological barriers, along with additional side effects, including gastrointestinal discomfort and emesis, are a major concern for patients undergoing chemotherapy. [3,4]

The results of several cancer research investigations have consistently shown that nanoparticle-based techniques facilitate targeted delivery to tumour cells, which can significantly improve and accelerate therapeutic outcomes. [5] The incorporation of nanotherapeutics into cancer treatment aims to address limitations related to other frequently employed delivery methods in therapy. [6]

Nanotechnology has emerged as a potential approach which involves precise control of elements at nanoscale level, featuring nanocarriers that exhibit unique and significant characteristics due to their nanoscale size. [1,7]

Nanocarrier-based techniques have shown positive outcomes in the management of cancerous tumours by enhancing drug movement in the body and delivering them more accurately to target cells, while reducing treatment-related toxicity, improving solubility, and stability of drugs. [8]

Nanocarriers enable targeted destruction of cancer cells while enhancing treatment specificity via dual targeting approaches such as the ligand-receptor interaction. Moreover, these systems are often functionalized with specific ligands to enable specific targeting capabilities. [9]

Recent developments in nanocarrier designs, including stimuli-responsive systems, multifunctional carriers, and other emerging strategies, have shown remarkable potential to improve overall therapeutic efficacy, leading to new possibilities for next- generation treatment approaches. This paper provides an extensive summary of various nanocarrier systems used in cancer therapy, highlighting their types, recent advancements, and associated challenges, and is discussed within the field of nanomedicine. [10]

Nanocarriers used in cancer therapy:

Various innovative nano-based drug delivery methods, as shown in Figure 1, are used for targeted administration of chemotherapeutic agents. Several significant carriers are examined in the following sections, highlighting their roles in cancer treatments.

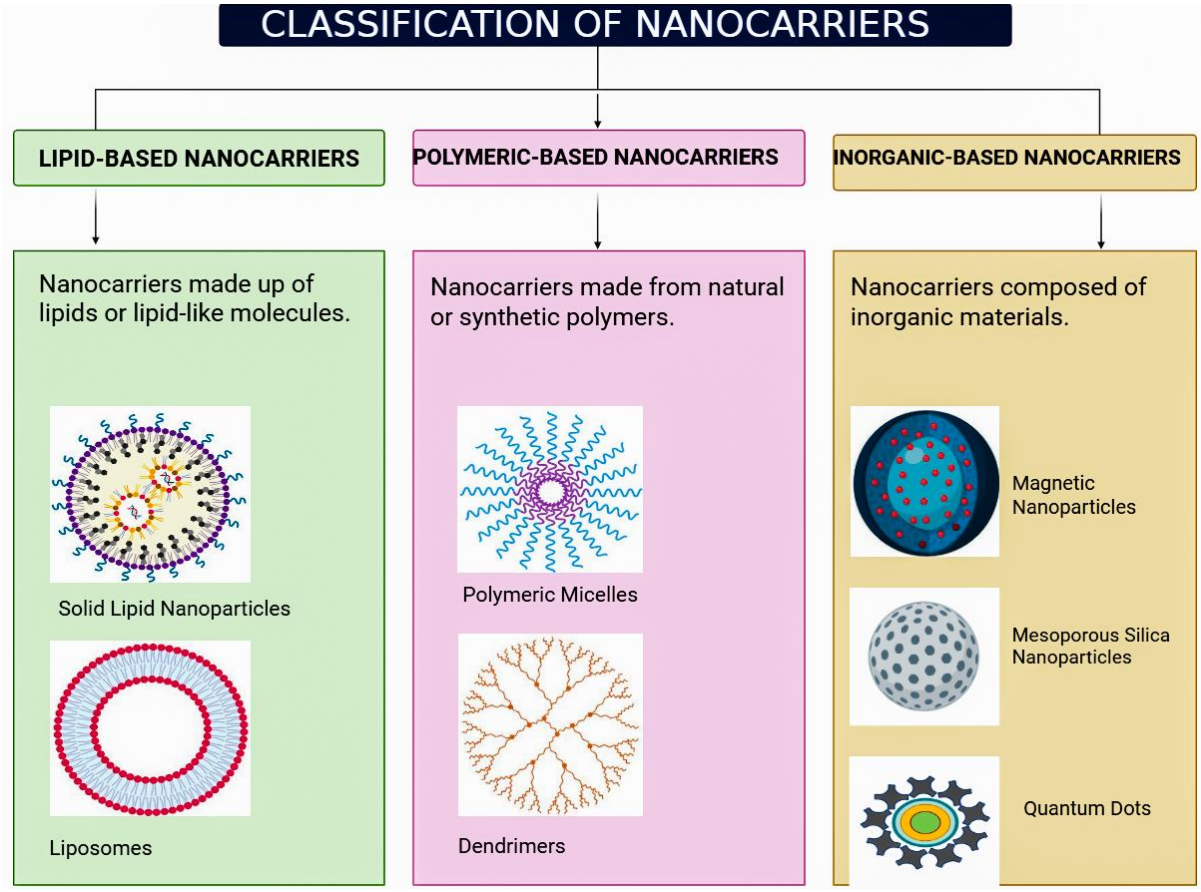

Figure 1: Classification of nanocarriers

1. Lipid-based nanocarriers

- **Liposomes:**

These are nanosized, round structures made of a lipophilic compound arranged in a double formation. These systems are capable of loading hydrophilic medications within their layers. They also help to protect the drug and improve its delivery. [11]

Liposomal forms of anti-cancer medications help deliver the medication directly to solid tumour sites with reduced toxicity. This helps to protect healthy cells and reduce side effects. They make the drug more stable and release it more slowly in the body in a controlled way, making the treatment more effective and safer. [12]

Pharmacokinetics of liposomes examines their distribution within bodily fluids and tissues, as well as their metabolic processes. The latter primarily involves the chemical breakdown and elimination of liposomes, accomplished through their uptake and removal by the RES. [13]

Merits-

They are highly compatible with biological systems.

They do not cause toxic effects in the body as they are similar to the natural cell membrane.[11]

Demerits-

The drug moves slowly in the body, which causes reduced effect at the site.

They tend to break down easily, which lowers their stability.[11]

- **Solid Lipid Nanocarriers (SLNCs):**

This system is mainly used to deliver medication throughout the body and to specific areas. Its unique features make it more suitable for delivering medications

in different ways. They can be used for both injections and oral use to produce an effect throughout the body. They are also useful in local treatments of specific regions such as the eyes, lungs and skin, which improves effectiveness and causes minimal side effects. [14]

Solid lipid particles are very small, tiny (50-1000 nm) in size, consist of body- friendly lipids that break down naturally and are generally safe for use. They are easily accepted by the body and provide several advantages over other methods. [15]

At present, several formulations based on this technique have been developed for various therapies, as these systems can carry different types of drugs, so they are capable of delivering both chemotherapy drugs and a wide variety of therapeutic agents. Furthermore, altering SLNs facilitates efficient active targeting towards the desired cells/tissues, enhancing treatment specificity and minimising secondary adverse effects. [16]

Merits-

These carriers do not show any toxic effects in the body, even when used for a longer duration.

Drug stability improves.[15]

Demerits-

The particles may form clumps, which can affect their performance.

The drug is released too quickly at once, which can reduce effectiveness.[15]

2. Polymer–based nanocarriers:

- **Dendrimers:**

Dendrimers are symmetrical, extensively branched polymers featuring a dense spherical form. They are typically created from a central polyfunctional core through the repeated addition of monomers. [17]

Owing to their nanoscale dimensions, they provide a mechanism for the eradication of issues observed in the implementation of treatments, as they can associate with a drug in various manners, including covalent or non-covalent interactions. [18,19]

The clearly defined 3D shapes and many outer groups enable loading of molecules within the cores of the dendrimers, as well as being connected to the surface groups mentioned previously. Dendrimers are capable of operating as drug transporters by enclosing medications within the dendritic configuration or by engaging with medications at their terminal functional groups through electrostatic or covalent links, creating a prodrug. [20]

Merits-

Easily dissolves in water, which helps in better drug delivery.

Safe and easily accepted in the body.

Capable of delivering a variety of therapeutic agents.[11]

Demerits-

The drug does not release at a controlled rate.

The drug gets cleared from the body too quickly.[11]

- **Polymeric Micelles:**

These are usually around 100nm and are designed in such a way that they focus on a particular cancer region using different triggers while avoiding quick renal elimination. [21]

Micelles were constructed from biodegradable and biocompatible block copolymers for drug delivery. The polymeric micelles have surface features that allow linking of pilot molecules. [22]

Polymeric micelles have surfaced as a valuable nanocarrier system for transporting poorly soluble anticancer drugs. Polymeric micelles offer various benefits, improve stability, and carry drugs effectively to the desired location. [23]

Drug targeting using a variety of polymeric micelles helps the drug reach and stay at the target site for better treatment, which selectively concentrates on utilising poorly water-soluble drugs within cancerous cells. [24]

Merits-

The outer groups can be attached to a specific target molecule, which helps in directing the drug to the desired cell.

It improves the solubility of fat-soluble drugs, which enhances their effectiveness. [11]

Demerits-

Limited capacity to load drugs, so only a small amount can be delivered.

This system works only with fat-soluble drugs, which reduces its versatility.[11]

3. Inorganic nanoparticles:

Inorganic nanocarriers have garnered significant interest in drug delivery because of their distinctive physicochemical characteristics and therapeutics capabilities.

A key benefit of these carriers is their significant drug-loading capability, imaging features, magnetically directed delivery and capacity to support hyperthermia-focused cancer treatment.[25]

- **Mesoporous Silica Nanoparticles:**

MSNs are frequently used for drug delivery due to their customizable structural features. The ability to modify pore size, surface area, and allow for chemical functionalization allows for effective transport of numerous types of therapeutic agents.[26]

These tunable nanostructures possess a high surface area and large pore size, making them excellent carriers for drugs. Due to the functional versatility of MSNs, researchers have developed multifunctional nanomedicine systems by integrating MSNs with other types of functional materials to produce enhanced carrier

theranostic devices (diagnostic devices that also act therapeutically) and ultimately achieve improved therapeutic results.[27]

- **Quantum Dots:**

Quantum dots, or QDs, are ultrasmall nanocrystals with the property of having reduced motions for charge carriers (holes and electrons) confined to nanometre-scale dimensions. Quantum dots possess discrete energy levels; therefore, their light-emitting and electrical characteristics are determined by their size.[28]

Advancement within these carriers with distinctive characteristics offers significant potential for cancer diagnosis and therapy. These types of (nano) materials can be readily modified or attached to biomolecules to fulfil specific needs in the field of biomedicine, thus allowing for the use of these types of (nano)materials as multifunctional platforms. Additionally, there has been a significant amount of research demonstrating that incorporating therapeutic drugs into QD-based systems increases their efficacy and improves the treatment outcomes.[29]

The presence of many functional groups on carbon quantum dots (CQDs) allows for bonding with different biological species. CQDs have been gaining popularity for use as a detection tool in immunofluorescent assays, where you are able to determine the presence of a particular cell type, tissue type, or sample and visualize the results of this detection in a short amount of time through the use of rapid detection methods that use CQDs. Additionally, the use of CQDs provides an ideal platform for the immobilization of biological species, allowing for the development of hybrid nanomaterials that will detect cancer-related antigens and tumour-associated biomarkers.[30]

- **Magnetic Nanoparticles:**

These delivery systems are composed of metal or oxide nanoparticles, which are capable of being directed towards the target site using a magnetic field. This helps in delivering the drug directly to the required area, improving treatment effectiveness and reducing side effects. [31]

These special carriers help deliver medicines directly to tumours and can also generate heat, which induces tumour tissue death. Magnetic particle dimensions, electrical charge, and surface characteristics. Chemistry is especially crucial as these factors exert a considerable influence on their blood flow duration and their availability within the body. Moreover, the dimensions have a significant effect on the properties. These demonstrate consistent drug accumulation inside the cells along with a dosage-dependent anti-growth activity. [11]

Merits-

Highly biodegradable

Minimal toxicity [11]

Demerits-

Expensive raw material

Low dispersion [11]

Mechanism of targeting and drug delivery:

There are different approaches for administering agents to specific targeted cells. One important method is Active targeting, where special molecules bind to receptors on cells to achieve localised action. Another method is Passive targeting, which works based on the natural tendency of some tissues to allow nanoparticles to enter and stay there for a longer time, which helps the drug to preferentially localize at the intended location, as illustrated in Figure 2. [32]

1. Active targeting

Active targeting consists of altering nanocarrier surfaces by adding specific molecules or antibodies that recognise and bind to particular site overly present on target cells, thus facilitating the accurate delivery of therapeutic payloads. [33]

Active targeting is used as an additional approach to passive targeting and is especially useful when drug accumulation at the target site is low, as it improves binding to target cells and helps overcome drug resistance. [34]

Advantages- Improved efficacy

Lower toxicity

Highly selective nature

2. Passive targeting

The physicochemical characteristics of nanocarriers, including shape, rigidity, and charge, effectively interact with anatomical and physiological conditions, thereby aiding their delivery to particular organs without requiring alterations to surface ligands. [35]

Passive targeting of a formulation typically works on the ability of drug carriers to enter and remain at the target tissues for a certain time. This is influenced by the physical characteristics of the carrier, which help in better accumulation at the intended location. [36]

Drug carriers are designed to circulate in the bloodstream for an extended duration, gathering at pathological locations characterised by compromised, leaky blood vessels (tumours, inflammatory sites, and infarcted regions), and enabling delivery of specially modified medications that can recognise and bind to particular cells that are difficult to access. [37]

Advantages- Enhanced bioavailability

Lower systemic toxicity

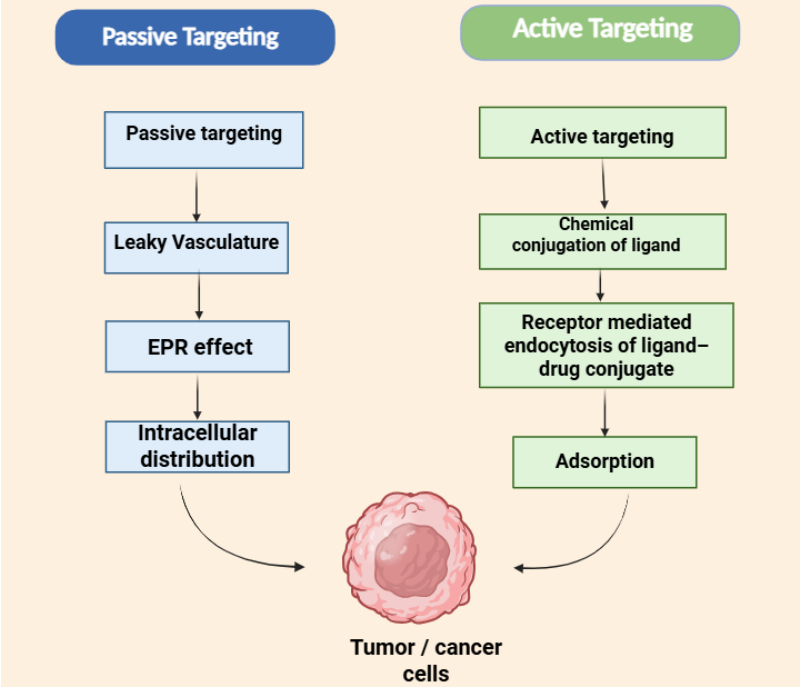

Figure 2: Mechanism of drug targeting in cells

Advances in nanocarriers:

1. Stimuli-responsive nanocarriers

These particular nanocarriers enables alterations and developed respond to different

external and internal changes. These changes can occur in their physical properties, which helps in better control of drug release. [38]

Stimuli-responsive nanocarriers minimise the intense negative impact of therapeutic agents, thereby improving treatment compliance and enabling regulated drug release at tumour locations. Consequently, the advancement of stimuli-responsive nanocarriers is essential in transporting drugs for cancer treatment. [39]

2. Bioinspired nanocarriers

Bioinspired nanocarriers are emerging as revolutionary instruments in drug delivery, utilizing natural biological structures and functions to address significant challenges of traditional therapeutic systems. [40]

Moreover, these systems are intended to optimise the delivery of drugs and genetic material to facilitate their acceptance in the body. These systems significantly impact the body systems due to their excellent traits, causing fewer harmful effects and binding capabilities. [41]

3. Nanocarrier in immunotherapy

Immunotherapy using nanotechnology targets immune cells in lymphatic organs, which in turn affects cancer cells, helps improve the body's ability to combat cancer through multiple treatment actions. [42]

Moreover, these systems allow the delivery of multiple agents together at the same time, which helps prevent immune system regulators and modify the tumour surroundings. They modify immune cell structure and function, which improves anticancer activity. [43]

4. Multifunctional Nanocarriers

These advanced systems, when combined with other medications, have the potential of targeting particular regions of the brain, thereby improving treatments. These nanocarriers can certainly be modified with medications and fluorescent agents, making their diagnostic and therapeutic possibilities tremendous. Imaging of molecular activity and function is at the forefront of ongoing research initiatives to identify and examine various diseases, including cancer, in a minimally invasive manner. [44]

Future Directions:

Promising fields within the study of nanocarriers encompass patient-specific treatment approaches and the development of advanced methods that help in both the identification and treatment of diseases, resulting in improved accuracy and effective therapies. [45]

- In cancer treatment, specific biomarkers and genetic mutations are essential for informing clinical choices. [46]
- The incorporation of intelligent technology into drug delivery systems facilitates real-time oversight, permitting treatment modifications and resulting in enhanced therapeutic results.
- Machine learning models powered by AI have been utilised to forecast delivery efficiency, facilitating the swift and methodical creation. [45]
- Moreover, advanced computer-based methods allow the use of nano-based medicine in medical practice forecasting, with the ideal physical and chemical characteristics suited to different types of tumours.

Advanced instruments provide a systematic route to develop nano-sized carriers which match individual tumour biology and therapeutic requirements, thus aiding in the creation of a more accurate and effective system that supports patient-specific treatment. [45]

Challenges in nanocarriers:

1. Physiologically diverse system

For therapeutic agents to effectively enter the cell and achieve the desired results, the carrier must quickly escape from internal cell sections and avoid the breakdown of the drug by enzymes. [45]

2. Toxicity risks and stability limitations

Because of their distinct physicochemical characteristics, these carriers may behave differently inside the body. They can react with the body in unforeseen manners, leading to possible toxic effects like non-selective biomolecule interaction and buildup in organs. Stability is an essential element affecting effectiveness in living systems. On contact with different organs, nanoparticles may aggregate or degrade prematurely, decreasing their circulation duration and changing their biodistribution. [45]

3. Regulatory challenges

Clinical translation of nanocarriers remains difficult because of the absence of consistent and biologically relevant criteria for testing and maintaining standards. [35]

4. Challenges in large-scale production

Nanocarriers are extremely vulnerable to various physical and chemical alterations during storage, creating significant obstacles to commercial production. Due to oxidation, changes can occur in the electric charge on the surface, which reduce the stability of particles and lead to the formation of harmful substances, which may diminish the effectiveness. [45]

Conclusion

Numerous studies highlight the capability of nanocarriers to effectively target and deliver anticancer agents. Despite these advancements in the field of nanocarriers, the heterogeneous and intricate biology of cancer still limits the ability to attain optimal drug delivery and distribution.

Emerging technologies, including smart nanocarriers, stimuli–responsive release, and multifunctional nanocarriers, have the ability to overcome challenges and difficulties in cancer treatments related to high systemic toxicity, drug resistance and inefficient cellular targeting. These advancements are leading to better clinical outcomes and safer cancer management. Advances in materials science, targeted drug delivery strategies to tumour cells, along with improved comprehension of biological systems, are required to enable efficient use of nanocarriers in cancer therapy.

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