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NANOMEDICINE: ADVANCES IN TARGETED DRUG DELIVERY SYSTEMS USING NANOPARTICLES IN CANCER TREATMENT

Shaik Khadar Mastan*, Sk. M. Allabakshu, Chandu Babu Rao
Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur-522017, Andhra Pradesh, India

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Abstract
Nano medicines offer a promising alternative for cancer treatment due to their nanoscale size, enabling precise site-specific drug delivery, higher bioavailability, and fewer toxic side effects. They allow the use of smaller drug doses, leading to cost savings. Gold Nano shells were among the earliest successful Nano therapies, demonstrating effective active and passive targeting. Unlike conventional drugs, Nano medicines degrade slowly, improving therapeutic outcomes. Various nanomaterials, including organic, lipid, inorganic, and polymer-based systems, are used. Their increased stability, controlled drug release, and biocompatibility enhance safety and efficacy. Ongoing preclinical and clinical research continues to advance Nano medicine for safer and more effective cancer treatments. Cancer is known as the most dangerous disease in the world in terms of mortality and lack of effective treatment. Research on cancer treatment is still active and of great social importance. Since 1930, chemotherapeutics have been used to treat cancer. Smart nanoparticles, which can respond to biological cues or be guided by them, are emerging as a promising drug delivery platform for precise cancer treatment. The field of oncology, nanotechnology, and biomedicine has witnessed rapid progress, leading to innovative developments in smart nanoparticles for safer and more effective cancer therapy.

Keywords: Nanomedicine, Targeted drug delivery systems, Lipid-based drug delivery, Cancer cells.

***Corresponding Author**
Shaik Khadar Mastan

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Introduction
Nano medicine is a promising field for developing targeted drug delivery systems for various diseases, particularly cancer cells. Lipid-based Drug delivery uses nanoparticles to encapsulate and deliver drugs to Specific cells or tissues, with researchers focusing on cancer cells due to their high proliferation rates and evasion of traditional treatment Methods [1].

To ensure the effectiveness and safety of these nanoparticles, extensive research and optimisation efforts are being conducted to fine-tune their size, surface charge, and composition. Researchers are also investigating their potential toxicity and biocompatibility to ensure their safety in clinical applications [2]. Nanotechnology has become an innovative method to treat various diseases, owing to its high potential and treatment efficacy in different cancer types. Cancer nanomedicine has wide applications in effective tumor therapy, based on targeting, imaging, viral nanoparticles, and enhanced delivery [3].

Nanotechnology simplifies the processes involved in food and agriculture, allowing better control of their production. This approach has great potential in the application of pharmaceutical chemistry for the production of nanomedicines to treat many diseases, including cancer, which cause millions of deaths annual worldwide. Nanomedicine involves the production of miniaturesized products with idea- properties, including reduced degradation time and decreased toxicity [4].

Nowadays, different types of cancer are observed among the population, indicating a high death rate and increasing live cases among children. The mortality rate of several cancers and extrapolated future projections are shown in Fig. 1. According to World Health Organization (WHO), there were 10 million deaths attributable to cancer in 2020, and each year approximately 400 000 children develop cancer. It is expected that by 2040, new cases will rise to 29.5 million with 16.4 million cancer-related deaths [5].

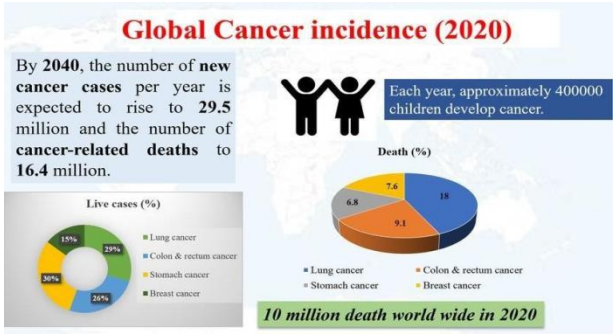

Fig. 1 The global incidence of cancer in 2020. Source: World Health Organization.

The importance of drug delivery in nanomedicine

Nanoparticles have shown great promise in improving drug delivery systems, allowing for the targeted and controlled release of medications. This has the potential to enhance the efficacy and reduce the side effects of drug therapies. Encapsulating drugs within nanoparticles protects them from degradation, delivers them directly to the target site, and releases them in a controlled manner, maximizing therapeutic effects [6]. Additionally, the use of nanotechnology in drug delivery has opened up new possibilities for delivering drugs to previously inaccessible areas of the body, such as crossing the blood-brain barrier for neurological disorders. This breakthrough technology has the potential to transform the field of medicine and significantly improve patient care [7].

Furthermore, nanoparticles can be engineered to release drugs in a controlled manner, ensuring a sustained and prolonged therapeutic effect. One potential drawback of nanoparticles in targeted drug delivery is the development of drug resistance in tumour cells. Over time, tumour cells can adapt and become resistant to the chemotherapy drugs carried by nanoparticles, limiting their effectiveness in treating cancer [8].

Origin and history of cancer nanomedicine

The early history of nanomedicine may be dated back to ancient times when colloidal gold particles were used for medicinal purposes [9]. Nanomedicine in its current form has been considered a possibility ever since the concept of nanotechnology was first introduced in 1959 by richard feynman in his caltech talk, "there is plenty of room at the bottom". He mentioned that it would be possible to arrange the atoms as desired. Nanomedicine can be defined as nano technology, which deals with the size range of 1 to 100 nm, applied to health and medicine [10].

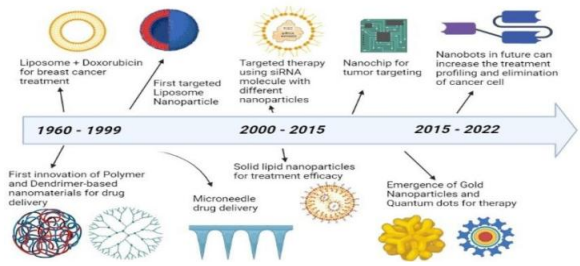

Fig. 2 timeline of cancer nanomedicine

Cancer therapy based on nanoparticles began with the development of doxorubicin loaded liposomes for treating breast cancer. Later, polymers and dendrimers came into use. Between 2000 to 2015, sirna molecules with different nanoparticles and solid lipid nano particles were developed for targeted therapy and treatment efficacy, respectively [11]. Nanomedicine is a pioneer field of nanotechnology that deals with the development of powerful techniques for treating diseases and for delivering certain biological compounds for treatment. An injection is the only method of administration for biologics such as peptides, therapeutic proteins, and antibodies (with a few exceptions). Nano-drug delivery has intensified efforts for development of painless injections, targeted treatment, and an increased ability of the drug to penetrate the bbb (blood brain barrier) [12].

Types of nanoparticles used in drug delivery

Nanoparticles, like liposomes, polymeric nanoparticles, and metallic nanoparticles, can be used to make different kinds of drug delivery systems that work well for certain types of cancer cells. Polymeric nano particles, made from biocompatible polymers, provide a safe and efficient means of drug delivery, while metallic nanoparticles, like gold or silver, offer unique optical and physical properties for targeted drug delivery and imaging [13].

➢ Inorganic nanoparticles

Inorganic nanoparticles, like gold and silver nanoparticles, have shown great promise in cancer treatment due to their unique properties. These nanoparticles can be engineered to target cancer cells and enhance the effectiveness of other treatments like chemotherapy or radiation therapy.

However, extensive research is needed to optimize their safety and efficacy profiles. Understanding the potential long-term effects of nanoparticles on the human body is crucial to preventing unintended harm to patients [14]. They must ensure that the benefits outweigh any potential risks and that patients are fully informed about the use of these innovative therapies. Moreover, collaboration between scientists, clinicians, and regulatory agencies is crucial to establishing guidelines and regulations for the safe and responsible use of nanoparticles in clinical settings [15].

➢ Organic nanoparticles

Organic nanoparticles are a promising alternative to metallic nano particles in medical applications because they are biocompatible and can be made to have specific properties, such as the ability to deliver drugs to specific areas or be used as an imaging agent [16].

Hybrid nanoparticles

Hybrid nanoparticles are a promising approach to addressing concerns about organic nanoparticle accumulation by combining the ad vantages of organic and inorganic materials. By incorporating inorganic components like metals or metal oxides, these nanoparticles can enhance their biocompatibility and reduce the risk of long-term accumulation [17].

Lipid-based nanoparticles for drug delivery

Lipid-based nanoparticles are a promising approach for drug delivery due to their biocompatibility and ability to enhance drug stability, solubility, and targeting capabilities. These nanoparticles can be designed to interact with resistant tumour cells, increasing their effectiveness and overcoming multidrug resistance (mdr) in cancer treatment. Nano particles made of lipids can get around efflux pumps on mdr tumour cells [18].

Polymer based nanoparticles for drug delivery

Polymer-based nanoparticles offer a promising approach to overcome Limitations in drug delivery systems. These nanoparticles can be designed with a controlled release mechanism, allowing for sustained drug release Over time. The size and surface properties can be tailored to enhance Stability in biological environments and targeting capabilities. This allows researchers to accurately study drug behaviour and toxicity in humans, leading to safer and more effective therapies. Polymer-based nanoparticles can be easily functionalized with ligands or antibodies to specifically target diseased cells or tissues [19].

Drugs are loaded into nanoparticles

Drug loading methods in nanoparticle synthesis include encapsulation, adsorption, and drug conjugation. Encapsulation allows controlled drug release, while adsorption involves drugs being adsorbed onto the surface of pre-formed nanoparticles. Encapsulation also protects the drug from degradation and enhances its stability. Nanoparticles can be modified to improve their interaction with biological systems, making them easier for cells to absorb and enhancing therapy
effectiveness [20].

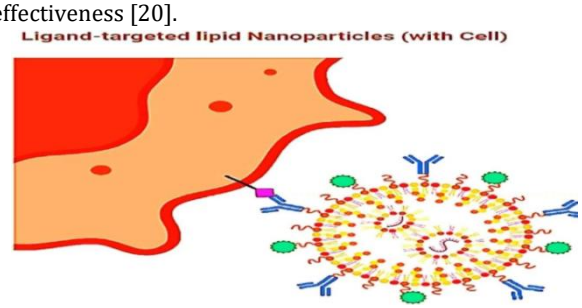

Fig. 3. Ligand-targeted lipid nanoparticles

Nanotechnology is being used in various applications, including targeted delivery systems, cancer imaging, and diagnostic tools. These systems use ligands or antibodies to bind to overexpressed receptors in cancer cells, allowing nanoparticles to accumulate in tumour tissue and avoid healthy cells. Additionally, pH-responsive nanoparticles can sense the acidic environment of tumours and release their cargo only in specific locations, improving the effectiveness and safety of cancer treatments [21]. Drug delivery systems are also being developed to target cancer cells specifically, minimising side effects and maximising chemotherapy drug effectiveness (Fig. 4). However, not all cancer biomarkers are specific to a specific type of cancer, leading to potential false positives or misdiagnosis [22].

Latest updates

Clinical trials are the last stage of drug development where in the drug formulations are tested on humans to determine their actual efficacy and side effects, to obtain approval for commercial use of the drug formulation.99 There are various phases for the clinical trial of a drug and all of them have to be cleared sequentially for the drug to be approved for medical use against the disease. The duration of each phase, the conditions involved, and the number of people the drug is tested on at each phase is decided by the drug regulatory authority. However, there mostly involves four phases of clinical trials before a drug is approved for medical use.

- **Status of approved drugs and those under clinical trials:**

Phase I of a clinical trial involves less than a hundred people and may include healthy people as control groups as this phase is to determine the safety and dosage of the drug. However, for cancer related drug trials, it is mandatory that the group includes people with that particular type of cancer. After clearing phase I, the drug can enter phase II clinical trials which is conducted on a few hundred people with a particular cancer. The objective of this phase of the clinical trials is to determine the efficacy and side effects. Therefore, it is common to have double blind studies with placebo control groups for this phase. The next phase also is aimed at determining the side effects. However, the focus is on long term and less common side effects and therefore include a larger study group of up to a few thousand people and can go on up to 3–4 years. Upon successful completion of phase III clinical trials, the drug formulation can be approved and may be marketed for medical use. However, the monitoring continues as phase IV wherein any and all adverse reactions reported are investigated for determining the overall safety and efficacy of the drug [23].

- **Approved nano-formulations for cancer therapy:**

Nano-formulations have been marketed for medical use against cancer since early 90's with the polymer–protein conjugate Zinostatin stimalamer being approved in Japan against hepatocellular carcinoma and the pegylated liposome Doxil® which was marketed as an anti-ovarian cancer drug formulation in the United States of America.101 With time, many other types of nano-formulations including liposomes, metal and metal oxide nanoparticles, polymeric micelles, and lipid nanoparticles have been developed and cleared for medical use by multiple agencies all over the world, with many more under various stages of clinical and preclinical trials. Table 1 gives a list of nano-formulations and the drugs used in them, which have already been approved for medical use. Doxil® was the first liposome to get approval in the US in 1995 for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma. After a year, NeXstar Pharmaceuticals developed daunorubicin-loaded NPs (DaunoXome®) to

treat HIVassociated Kaposi sarcoma. In 2000, Myocet® is another formulation that contains doxorubicin and cyclophosphamide and got EMEA approval for treating metastatic cancer. Later, Marqibo® got FDA approval for treating nonHodgkin's Lymphoma and leukemia. In 2013, Lipusu was developed by incorporating paclitaxel for treating gastric, ovarian, and lung Cancers [24].

Trade name	Compound	Nanocarrier
Abraxane	Paclitaxel	Albumin bound paclitaxel
DaunoXome	daunorubicin	Pegylated Liposome
Doxil	doxorubicin	Pegylated Liposome
Bexxar	anti-CD20 conjugated to idodine131	Radioimmunoconjugate
Zevalin	anti CD 20 conjugated to yittrium-90	Radioimmunoconjugate
Zeladex	goserelin acetate	Polymer rods
Myoset	doxorubicin	Non-pegylated liposome
Oncasper	PEG-L-asparaginase	Polymer-protein conjugate
Ontak	IL-2 fused to diphtheria toxin	Immuno toxin fusion protein
SMANCS	Zinostatin	polymer protein conjugate

Table-1: Approved nanomedicine drugs in the market for cancer treatment

Future challenges

The lab-scale production of drugs are easier to achieve, but large-scale manufacturing seems to be a challenging task due to limitations in the advanced experimental set-up and nonavailability of sufficient information on the scale-up technologies. Also, adverse effects are encountered due to the difficulties observed during the scale-up process and in reproducing the preparation process [25]. Opportunities and challenges are two sides of a coin. More clinical trials are needed for the confirmation of preclinical and in vitro studies. These should help develop a deep understanding of the interaction of nanoparticles with cells and its after-effects. The main drug delivery routes are oral, intravenous, and subcutaneous for anticancer administration. Inhalation delivery, rectal delivery, and pulmonary delivery are newly proposed. However, these methods are limited due to the high toxicity caused by the combined action of drug deposition and high therapeutic potency. Besides, massive drug doses are needed due to the loss of drugs in the pulmonary tract. In rectal delivery, low absorption is also a major problem [26].

➢ Cancer nanodrug delivery challenges

Cancer nanodrug delivery faces significant challenges due to the immune system's ability to eliminate nanoparticles or build them up in unintended tissues, reducing their effectiveness. The dense extracellular matrix and abnormal blood vessels in a tumour's microenvironment make it difficult for nanodrugs to reach and spread through the tumour [27]. To overcome these obstacles, targeted drug delivery systems are developed by incorporating targeting ligands onto nanoparticle surfaces that specifically recognise and bind to tumour cell receptors. This approach enhances therapeutic efficacy while minimising off-target effects. Various targeting ligands, such as antibodies, peptides, and aptamers, have been explored for this purpose [28].

Conclusion

Targeted drug delivery systems have shown promise in enhancing cancer treatment, but tumour heterogeneity and microenvironmental difficulties limit their efficacy. Further research and development are needed to optimise targeted therapy delivery.

In the past years, nanotechnology has been widely applied in all aspects of science, engineering, and technology, and research & development in this discipline has been intense. Many cancer nanomedicine researchers have investigated largely consistent processes, which include formulation, characterization, in vitro proof of concept, and validation of anticancer activity in preclinical trials. In conclusion, a variety of smart nanoparticles are being used or have the potential to be exploited as drug delivery systems for advanced cancer therapies.

Author Contributions

All authors are contributed equally

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Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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