NANOPARTICLE DRUG DELIVERY SYSTEMS FOR TARGETED CANCER THERAPY.

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This Report Presented in Partial Fulfillment of the Requirements for the Degree of Bachelor of Science in Computer Science and Engineering

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APPROVAL

This Project/internship titled **"Nanoparticle Drug Delivering Systems for Aimed Cancer Therapy"**, submitted by, **Md. Mehedi Hasan Nayon,** to the Department of Computer Science and Engineering, Daffodil International University has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of B.Sc. in Computer Science and Engineering and approved as to its style and contents. The presentation has been held on.**13/07/2024**

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We hereby declare that this project has been done by us under the supervision of **Dr. Shake Rashed Haider Noori, Professor & Head, Department of CSE Daffodil International University.** We also declare that neither this project nor any part of this project has been submitted elsewhere for the award of any degree or diploma.

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ABSTRACT

The exploration of nanoparticle medication transport structures is an unexpected methodology in the field of oncology that offers gigantic benefits over traditional cancer remedies. The postulation investigates the advancement, mechanisms, and effectiveness of nanoparticle-based transport structures explicitly designed for aimed cancer treatment. The chief concentration is on the capability of nanoparticles to expand drug dissolvability, steadiness, and managed launch while diminishing antagonistic consequences on healthy tissues. Distinct types of nanoparticles, like liposomes, polymeric nanoparticles, metallic nanoparticles, dendrimers, and quantum dots, are analyzed for their different features and potential uses in cancer treatment. The benefit of these systems, like enhance therapeutic ability, lessen secondary results, and multifunctionality, is emphasized, together with the issue linked to biocompatibility, toxicity, production, and regulatory approval.

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CHAPTER 1
Introduction

1.1 Introduction

Cancer remains a global challenge, prompting the constant search for better treatment options. The fight against this disease has seen progress with various methods tailored to individual needs, enhancing effectiveness against malignant tumors. Chemotherapy stands out as a widespread approach in tackling cancer. While it operates through multiple mechanisms, its primary goal is to eliminate rapidly dividing cells – both healthy and cancerous – leading notable side effects like hair loss and digestive issues. Efforts have long been dedicated to refining treatments that specifically target cancer cells while sparing healthy ones. Despite advancements in targeted therapy, challenges persist. Adverse reactions sometimes accompany these treatments, alongside the looming threat of developing resistance. How can we overcome these hurdles and push the boundaries of cancer research further? This quest for answers fuels ongoing exploration and innovation in the field. At present, cancer is still the second most common reason for death, and existing treatments for numerous types of cancer are not sufficient. This is why more and more research is focusing on developing accurate cancer therapies and addressing drug resistance issues. Nanotechnology has become increasingly important in recent years, providing innovative solutions to various challenges by creating nanoparticle drug delivery systems. Nanop are tiny materials ranging in size from 1 to 100 nanometers, possessing distinct physical, chemical, and biological characteristics. These attributes allow nanoparticles to interact with biological systems on a molecular and cellular level, making them well-suited for drug purposes. Nanoparticle drug delivery systems have the ability to enclose therapeutic substances, safeguarding them from degradation while improving their solubility, stability, and availability. Additionally, these systems can be customized for precise and sustained release of drugs, ensuring a reliable therapeutic impact. Drug delivery systems often utilize nanoparticles selected for their specific size and properties tailored to the nature of the tumors. In cancer therapy, nano-carriers work by targeting tumor cells with the help of nanoparticles and the positioning effect of the targeting substance once absorbed. Following this, they release drugs to the tumor cells to induce cell death. These drugs encased within the nano-carriers consist of conventional chemotherapy drugs and nucleic acids, demonstrating their effectiveness in both cytotoxic and gene therapy approaches. Moreover, some drugs that are not easily soluble find a solution in NPs, which act as a platform to

encapsulate them and transport the drugs into the bloodstream. NPs, with their specific size and surface features, play a crucial role in boosting perme and retention, thereby prolonging the drugs' half-life and assisting in their accumulation in tumor tissues. Simultaneously, the targeting mechanism shields healthy cells from the harmful effects of drugs, thus reducing the negative impacts of cancer treatment. For instance, PEGylated liposomes carrying doxorubicin were found to decrease cardiotoxicity in comparison to free doxorubicin. Furthermore, nanoparticle albumin-bound paclitaxel resulted in fewer adverse effects and enabled higher doses to be tolerated than traditional solvent-based taxanes. Apart from chemotherapy and gene therapy, several studies have highlighted the use of NP drugs in immunotherapy and tumor ablation treatment. The application of nanoparticle-based drug delivery systems is anticipated to improve immunotherapy outcomes and reverse the tumor's immune-suppressing environment. An increasing number of nanotherapeutic medications have entered the market or reached the clinical development stage. In 2010, the initial phase I clinical trial utilized a targeted nanoparticle system to transport small interfering RNA (siRNA) patients with solid cancers. Another clinical investigation revealed better effectiveness in treating tumors with an actively targeted polymeric nanoparticle carrying the chemotherapeutic docetaxel (DTXL) compared to a solvent-based DTXL version. Progress has been made in developing hybrid for drug delivery systems, combining different nanoparticles' properties to enhance overall function and stability. Nanoparticles have also displayed advantages in addressing anti-tumor drug resistance, offering platforms for combination therapy and interfering with mechanisms like efflux transporters on cell membranes.

Among which, nanoparticle delivery system is a promising one to target tumors more accurately with minimum tissue damage. Passive and active targeting strategies THE BEST DRUG DELIVERY MODEL: Passive Targeting in Enhanced. The so called enhanced permeability and retention (EPR) effect ensures the accumulation of nanoparticles at tumor sites because of their leaky blood vessels. Conversely, active targeting involves the manipulation of nanoparticles to attach ligands or antibodies that will bind to cancer cell receptors thus increased treatment precision and effectivity. Nanoparticle drug delivery systems hold great promise in treating diseases, but many challenges remain as well. In addition, there are vital considerations to be made regarding biocompatibility, toxicity, manufacturing and regulatory approval in order for these technologies to achieve safe and successful translational potential from the laboratory through to clinical application. Exciting new developments in the field, including combination therapies, personalized medicine and

responsive nanoparticles hold promise that these barriers could be overcome to improve treatment outcomes for cancer. In the following, we analyze different types of nanoparticles for drug delivery: liposomes, polymeric nanoparticles, metallic nanoparticles, dendrimers and quantum dots. The prime reason for such diversity among SMMs is due to the fact that they each carry their individual unique features as well merits and demerits which obviously pose substantial influences on its utilization in cancer therapy. Drug targeting, delivery and release mechanisms are well investigated to know these systems improve therapeutic outcome in association with conceptualization of nanoparticle drug delivery for targeted cancer therapy showing its development prerequisites over conventional approaches and advantages besides recent efforts at overcoming ongoing obstacles in present time causing an as a whole recapitulative on themes related to designing and improvement.

1.2 Motivation

Despite significant advancements in early diagnosis and treatment options, cancer continues to be one of the main reasons for morbidity and mortality worldwide. These traditional cancer therapies like chemotherapy and radiation frequently disrupt all cells - not just the sick ones- causing serious side-effects, so this acts on a non-selective basis. As a result, the need to find more tailored and effective ways of treating these populations has spurred inquiry within the scientific community. The purpose of studying nanoparticle drug delivery systems (NDDSs) is their potential to completely change cancer therapy by providing a way for therapeutic agents to be delivered directly to the site of tumors, enabling an improved quality response rate without systemic toxicity. Their small size, high surface area to volume ratio, and ease of functionalization with different kinds of ligands due to use in targeting drug delivery are just a few unique features that point towards nanoparticles as good carriers. As the limitations of traditional therapies are directly addressed by NDDS, their maintenance seems to be an appealing and timely rationale for further investigation.

1.3 Objectives

The primary objective of this research is to explore and evaluate the potential of nanoparticle-based drug delivery systems in targeted cancer therapy. Specifically, this thesis aims to:

- Explore different typologies of nanoparticles used or under study for drug delivery purposes by describing their properties, preparation techniques, and functionalizing strategies.

- Evaluate the efficiency of NDDS in cancer cell delivery, such as how nanoparticles can selectively target tumor tissues and not healthy cells.
- Review the therapeutic effects of NDDS in preclinical and clinical trials, especially them helping to enhance bioactivity and decrease side effects along with better reach other drug by conventional therapy.
- Address the complications and constraints in NDDS application - these include (1) biocompatibility, (2) toxicity, and regulation-related burdens.
- Review the current state of the art NDDS, provide a future outlook, and discuss some potential directions in which the field is heading enabling us to have much more effective nanoparticle-based therapy for cancer.

The main goal is to investigate the ability of conventional as well as emerging nanoparticle-based drug delivery systems (NDDS) to target cancer therapy. The central idea of this thesis is to pursue an investigation into the different types of nanoparticles proposed or being used in drug delivery, their characteristics, fabrication processes, and functionalization techniques. The evolution of these systems has been directed towards their application for targeting cancer cells with specificity and selectiveness, in which nanoparticles preferentially reach tumor tissues using different strategies while reducing the damage to normal tissue. Hence, it aims to confirm how efficient such a response is in accomplishing this goal inside the nano-system. In addition, research is being conducted to determine the therapeutic effectiveness of NDDS and compare their bioavailability with other systems, as well as the beneficial role demonstrated in various human clinical trials over conventional therapies. In addition, the study will recognize and overcome some of the challenges, including toxicity issues and either biocompatibility or regulatory bottlenecks surrounding NDDS. Lastly, the research will conclude with a snapshot into future directions and prospective technological improvements in this area, which will identify new trends as well as breakthrough technologies that can take nanoparticle cancer therapy another mile further. The objectives set out in this research, if achieved, could provide critical advancements to the development and utilization of NDDSs as anti-cancer agents.

CHAPTER 2
Literature review

2.1 Literature review

Nanoparticles as drug delivery systems have a great potential in the successful chemotherapy and reduced side effects of cancer therapy. Earlier works of Dr. Torchilin and his colleagues Balis described how being entrapped in liposomes can enhance the pharmacokinetic properties of anticancer drugs as well as their biodistribution [1]. Recent works have further demonstrated the potential of other types of nanoparticle platforms for targeted drug delivery in cancer therapy, including polymeric nanoparticles, metallic nanoparticles, dendrimers, and quantum dots [2]. The clinical success of liposomal anticancer drugs combined with advancements in stealth liposomes (coated by polyethylene glycol, which prolongs circulation and enhances tumor targeting) have established drug delivery systems as excellent solutions to effectively deliver cancer therapeutics to kill both primary tumors and metastatic ones [3]. Polymeric nanoparticles, especially those made from poly(lactic-co-glycolic acid) (PLGA), have the ability to provide controlled drug release and increase tumor penetration [4]. Among metal nanoparticles, gold and silver are mainly used for imaging and therapy due to their unique optical and thermal characteristics [5]. Dendrimers and quantum dots are also used in targeted drug delivery and diagnostic imaging for cancer therapy [6].

Polymeric nanoparticles, such as PLGA-based NPs or PEG-NPs, are noted for their applicability in controlled drug release and enhanced tumor penetration [7]. The use of polymeric nanoparticles for long-term, localized drug release and targeted therapy was underlined by the study of Langer and co-workers [8]. Metallic nanoparticles like gold and silver are of special interest because the optical and thermal properties of metal-based nanoparticles make them useful for both imaging and therapy [9]. Studies by Huang et al. and Hirsch et al. have exploited the unique properties of gold nanoparticles for photothermal therapy, producing nanospheres able to vaporize cells in vitro upon localized heating [10]. Dendrimers are often used as drug carriers due to their high turnover and loading capacities, with the possibility to control exact time points for drug release [11]. Research by Patri et al. and Majoros et al. demonstrated the capability of dendrimer-based DDS to tackle multidrug resistance in cancer cells [12]. The emerging class of cancer diagnostic and therapeutic agents based on quantum dots, semiconductor nanoparticles with customizable optical properties, has also sparked increasing interest [13]. Studies by Michalet et al. and Gao et al. showed that

quantum dots could be useful for multiplexed imaging of cancer biomarkers and in vivo drug-targeting quantitation [14]. Additionally, Pinaud et al. demonstrated that quantum dots could detect unique fluorophore fragments while the drug was being taken up and delivered to its target site simultaneously [15].

Mechanisms of Targeting in Nanoparticle Drug Delivery: Nanoparticle drug delivery systems work only if they actually deliver drugs that will exclusively act on cancer and ignore healthy cells. One change is that due to impaired tumor vessel permeability as well as likely poor, if any, lymphatic drainage, a 'default' passive targeting mechanism for macromolecules has been created, which is known in the community as the Enhanced Permeability and Retention (EPR) effect. This effect was first described in a classic paper by Maeda and Matsumura [16], along with further studies on the EPR effect and its distribution in solid tumors by Yuan et al. [17]. Active targeting is accomplished by coating nanoparticles with molecules like ligands or antibodies that are capable of binding to receptors found on cancer cells to carry out the proper delivery of therapeutic payloads. These findings ultimately led to the introduction of active targeting approaches in cancer cell targeting, including tumor-homing peptides and more recently, tumor-targeting antibodies pioneered by Ruoslahti and associates [18].

Passive Targeting via the Enhanced Permeability and Retention (EPR) Effect: The EPR effect takes advantage of the long-known attribute that tumor vasculature is always leakier when compared to the normal vasculature and lacks functional lymphatic drainage. As a result, nanoparticles accumulate in tumor tissues preferentially. Maeda and Matsumura [19] and Yuan et al. [20] detailed the EPR effect and its potential application for NP-based drug delivery. Passive targeting may be enhanced by the optimization of nanoparticle size, surface charge, and circulation time for the tumor uptake while limiting off-target effects.

Active Targeting Strategies: Active targeting generally means coating the nanoparticles with antibodies or ligands that bind to receptors overexpressed by cancer cells, a phenomenon known as active targeting. The identification of tumor-homing peptides and antibodies for targeted drug delivery was revolutionary due to the studies conducted by Ruoslahti et al. Here, we developed a next-generation anti-EGFR nanobody engineered to facilitate strict tumour specificity and effective intracellular delivery of therapeutic payloads via peptide-mediated scaffold dimerization. Such advances hold great promise in the development of nanoparticles as drug delivery vehicles with enhanced specificity and effectiveness.

Compared with traditional cancer therapy, nanoparticle drug delivery can increase drug solubility, stability and bioavailability. Studies by Alexis et al. (2008) and Davis et al. Previous studies have implied that the utilization of NPs matrices could be promising in bypass drug resistance mechanisms and improving therapeutic activity (Hashizume, et al. Because individual nanoparticles can carry many different drugs, the technique can be used to deliver powerful combination therapies and customized treatment regimens. Despite this promising potential, significant challenges related to biocompatibility, toxicity testing, ease of manufacture at scale, and getting regulatory approval for these types of therapies in a timely manner still have to be overcome. Research by Nel et al. Both (2009) and Dobrovolskaia & McNeil (2007) stressed the need for careful pre-clinical characterization and safety assessment in order to avoid potential disadvantages of any nanoparticle-based therapy. The development of various nanoparticle-based drug delivery systems is the milestone in cancer therapy. Chemotherapy and other conventional cancer treatments tend to be nonspecific and cause collateral damage, involving the toxic side effects common with these types of therapy. Nanoparticles own excellent properties such as small size, uniformity and reproducibility which make them potential agents for cancer diagnosis and therapy via delivering drugs to the tumor regions by means of passive or active targeting effects. The initial applications of nanotechnology in drug delivery depended on the unusual characteristics of nanoparticles. The initial work by Torchilin, et al. (2003) had demonstrated the potential of liposomal formulations to alter pharmacokinetics and tumoral distribution of anticancer agents paving the pathway for further advances in nanoparticle-based drug delivery systems.

2.2 Types of Nanoparticles Used in Drug Delivery

Given their widespread use, the structures of iron oxide nanoparticles (IONPs) used in drug delivery are complex and multifaceted.

Liposomes: The use of liposomes as bilayers due to their biocompatibility and possible encapsulation of both hydrophilic and hydrophobic drugs is quite general. Studies by Gabizon et al. (1994) and Allen et al. Liposomal formulations have a wider therapeutic index since they minimize off-target effects while enhancing the drug accumulation in tumor tissues (Gabizon 2002). Even with the most recent advances in PEG modified stealth liposomes (Matsumura & Maeda, 1986) these delivery systems have limitations as reduced pharmacokinetics of encapsulated drugs to the target tumor site may be hampered due to limited drug release from long circulating blood pool.

Polymeric Nanoparticles: Polymeric nanoparticles, in particular nanosizes based on biodegradable polymers such as PLGA and PEG, hold great potential as corrugated drug carriers for controlled drug release and improved penetration within tumors [21]. Research by Langer et al. (2001) were the first to show that polymeric nanoparticles could be used for sustained drug delivery, and subsequent engineering of these nanoparticles have allowed control over drug release rates and intracellular uptake.

Metallic Nanoparticles: Gold and silver nanoparticles specifically have excellent optical absorbance and thermal properties that make them ideal for imaging and therapy purposes. Studies by Huang et al. (2006) and Hirsch et al. Jay, 2003) has established the possibility of using gold nanoparticles for photothermal therapy, by which heating of tumor cells is achieved through laser irradiation. It was also reported that silver nanoparticles have a potential use as anti-microbials and radiosensitizers in cancer therapy.

Dendrimers: Dendritic (tree-like) macromolecules offer high drug-loading capabilities and control over release profiles owing to their unique highly branched structures. Research by Patri et al. (2002) and Majoros et al. (2006) stated that dendrimers show great potential in drug delivery to subside multidrug resistance in cancer cells. In terms of translating dendritic micelle formation transition into their in vivo efficacy, several recent studies have been devoted to the production of tumor-penetrating and targeted nanomicelles by tuning dendrimer design and surface modification strategies (Lee et al. 2010).

Quantum Dots: Quantum dots (QDs) semiconductor nanoparticles with controllable physical dimensions have become versatile imaging and therapeutic agents for cancer. Studies by Michalet et al. (2005) and Gao et al. demonstrated that quantum dots could be applied to multiplexed imaging of cancer biomarkers and for real-time monitoring of drug delivery (2004). Many of the earlier concerns of nanoparticle toxicity have been resolved through more advanced surface coating and biocompatible formulations, making them candidates for future clinical trials (Hardman, 2006).

Recent research work extend nanoparticle-based drug delivery system towards combination therapies of multiple therapeutic agent to realize to obtain synergistic effect. Similarly, strategies like personalized medicine approaches for the optimization of nanoparticle-based therapies are also undergoing vigorous investigations. Research by Wang et al. In this line, the arriving of combination therapies and the possibility to apply individually adapted therapies have been pointed up by Almeida et al (2014), improving outcomes for leukemia patients. Nanotechnology Confers New Life to Cancer Therapy. This fully programmable

process allows yolk-shell particles to swank dual functionalities of stimulus response leading toward responsive nanoparticles which synergistically react on external stimulants such as pH/temperature changes for controlled release and targeted drug delivery precisely. Combining diagnostic imaging and therapeutic functions into the same platform can allow accurate and personalized monitoring (Chen et al., 2011), holding great promise for theranostic nanoparticles. Further directions of research involve utilizing artificial intelligence and machine learning in improving nanoparticle design, treatment response predictions and fast tracking therapeutic innovation in cancer nanomedicine.

CHAPTER 3
Research Methodology

3.1 Drug Delivery Systems

Nanoparticles revolutionized oncology as drug delivery system providing a platform for controlled drug release in tumor site. The use of nanoparticles for the preparation of drug delivery systems relies on their unique features that enable improved drug solubilization, prolonging its circulation time and targeting a specific tissue or cell by encapsulating therapeutic agents, enhancing therapy outcomes while minimizing systemic toxicity. Nanoparticle Drug Delivery in Cancer Therapy is mostly related to general knowledge of nanoparticle drug delivery systems and includes their design principles, fabrication methods, characterization techniques, and functioning for targeted cancer therapy. A few central concepts govern the design of nanoparticle drug delivery systems with the goal of improving therapeutic efficacy and reducing off-target side effects. At the heart of these principles are things like nanoparticle size, shape, surface chemistry, and bio-compatibility.

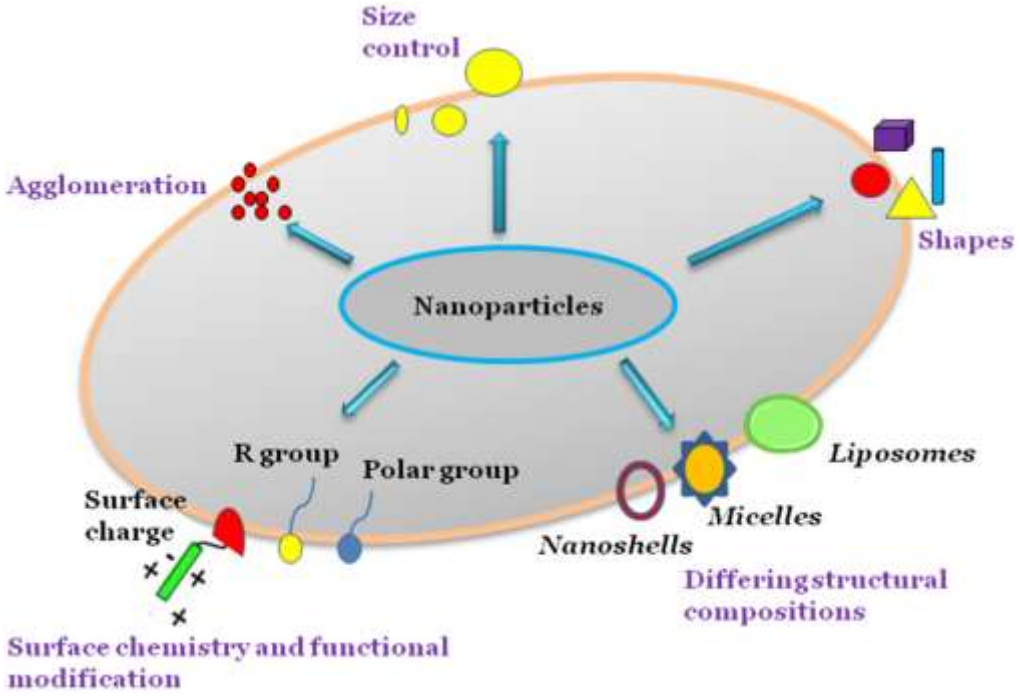

Figure 1.1: Drug Delivery Systems

Optimal nanoparticle biodistribution, cellular uptake, and therapeutic efficacy depends on their size and shape. Due to their 1-100 nm diameter, they can escape from the clearance mechanisms and accumulate in tumor tissues by passive targeting strategy based on Enhanced

Permeability and Retention (EPR) effect. On the other hand, rod-shaped and branched nanoparticles show better performances in cellular uptake and internalization processes, but they are hard to synthesize homogeneously in size. For example, nanoparticle surface functionalization with targeting ligands (e.g., antibodies or polymers) has been used to improve their specificity towards cancer cells and assist with modulation of their pharmacokinetic profiles. Versions of PEGylation (with polyethylene glycol) is one strategy to avoid immune recognition and to extend circulation time in the blood stream for better chance of reaching the tumor area (Suk et al., 2016). As a result, ligands (e.g., peptides or aptamers) that target these receptors are now conjugated with nanoparticles to further facilitate intracellular uptake and release of the therapeutic payload. High biocompatibility of nanoparticles is crucial to providing bio-effectiveness with minimal side effects, thus enabling potential clinical applications of the nanoparticles. Biodegradable polymers, PLGA and chitosan are widely used for drug encapsulation with toxicity-free degradation products in the body. The surface modifications using biocompatible materials and enhancement in particle size distribution are some of the factors which help to maintain stability and safety of the nanoparticle formulations within the biological environments.

3.2 Fabrication Methods of Nanoparticle Drug Delivery Systems

A variety of fabrication techniques are used to engineer the size, shape, and drug encapsulation efficiency of nanoparticle drug delivery systems. An example on how to govern nanoparticle properties is given with these methods, containing chemical, physical and engineering principles. Top-down methods are used to break materials bulk into nanoparticles through mechanical or chemical path. This is accomplished using methods as high-energy ball milling (HEBM) and lithographic technique making it possible to create nanoparticles with a controlled distribution of size and crystalline structure. And these techniques can be difficult to produce a consistent particle size and can be harmful for drug stability during the manufacturing. On the other hand, Bottom-up methods are those in which molecules or atoms are assembled to form nanoparticles, starting from the bottom. Due to the controlled synthesis of particles by chemical techniques like emulsion polymerization, solvent evaporation and self-assembly, it is possible to control the composition and hence surface properties of the nanoparticles (Zhang et al. 2008). These techniques enable hydrophobic and hydrophilic drugs to be entrapped in nanoparticle networks, improving loading capacities and release kinetics.

Nanoengineering Techniques: Nanoengineering approaches have emerged that bridge physics and materials science to design nanoparticle properties for desired applications. Particle engineering processes such as microfluidics and electro spraying enable the production of well-defined particle size distributions and morphologies which are suitable for targeted drug delivery (Cheng et al. 2010). Nanoscale patterning and 3D printing also provide new techniques to design complex nanoparticle architectures for the improvement of therapeutic functionalities

Characterization Techniques: The characterization of various properties of nanoparticle drug delivery systems plays a critical role in standardizing, quality control & understanding their biological interactions. The physicochemical properties, drug loading efficiency, stability, and in vitro/in vivo behavior of nanoparticles are examined by a series of analytical techniques.

Morphology and Particle Size: One of the maximum popular methods employed to look at size distribution and morphology is Dynamic Light Scattering, Transmission Electron Microscopy (TEM) respectively. On the opposite hand, DLS can measure common hydrodynamic size of debris in conformation, while TEM provide very excessive decision image and shape of nanoparticles.

Drug Encapsulation Efficiency: For these extensive techniques are available to measure raise of drug loading and encapsulation efficiency like High Performance Liquid Chromatography (HPLC), UV-Vis spectroscopy quantifying drug loaded and entrapped inside nanoparticles. They measure the quantity of drug encapsulated per unit mass of nanoparticles, and serve as a control to confirm that the drug loading procedure is reproducible.

Surface Charge and Composition: Nanoparticle surface charge, and chemical composition analysis is performed by zeta potential analysis and Fourier Transform Infrared Spectroscopy (FTIR). Zeta potential analysis sheds light on nanoparticle stability and their interactions with biological membranes while FTIR spectroscopy allows for the identification of functional surface modifications/groups and so on.

In vitro and In vivo Studies: The biological performance of nanoparticle drug delivery systems is evaluated using cell culture assays and animal models. In vitro studies evaluate cellular uptake, cytotoxicity and intracellular drug release kinetics which help gain the initial understanding of the efficacy and safety profile of nanoparticle (Yuan et al., 2016). In vivo investigations provide knowledge regarding pharmacokinetics, biodistribution, and biological

activity in animal models which paves the way forwards for clinical translation of nanoparticle-based therapeutics.

3.3 Targeted cancer therapy: Utilizing Nanoparticle Drug Delivery Systems

Amorphous nanoparticle Targeted drug delivery and combination therapies, which rely on nanoparticle-based drug delivery systems, have the potential to significantly improve cancer therapy efficacy and safety. In this section, we present instances of several kinds of recently created, and increasingly used, nanoparticle-based systems and compounds for oncological applications.

Chemotherapeutic drugs are more elegantly delivered to tumor sites thanks to nanoparticles, which also lessen systemic toxicity and improve healing outcomes. In comparison to free drug formulations, liposomal formulations such as Doxil, have improved pharmacokinetics and less cardiotoxicity. These formulations have been approved for research use. Immunotherapies based on nanoparticles such as immune checkpoint inhibitors and vaccines providing antigens through nanoparticles, aim to overcome immune evasion mechanisms in cancer cells and promote anti-tumor immune responses.

Photothermal and Photodynamic Therapy: Metallic nanoparticles such as gold nanorods and nano shells have superior absorption of near-infrared (NIR) light; they can convert optical energy into local heat through photothermal processes. This feature makes it the most conservative oncologic therapy by allowing a tumor cell removal and inhibiting any new tissue while maintaining normal tissues surrounding it. For instance, through photoactivation, tumor cells can stop growth and undergo apoptosis induced by the photodynamic treatment that uses photosensitive nanoparticles to generate reactive oxygen species (ROS) which help to eliminate tumors in a site-specific manner.

Gene Delivery and RNA Interference: Nanoparticles are used as effective carriers for nucleic acid-based therapies such as gene delivery and RNA interference (RNAi). Lipid nanoparticles and polymeric vectors protect nucleic acids from degradation, and carry them inside of the cells, to ultimately modulate gene expression in cancerous cells specifically. The development of nanoparticle-mediated RNAi therapeutics appears highly promising not only in silencing oncogenes but what might be the best use is for reversing drug resistance and boosting personalized cancer therapy.

Theranostic nanoparticles are capable of combining diagnostic imaging and therapeutic functionalities into one platform, allowing physicians to monitor treatment responses in real time and develop new personalized treatment strategies. Nanoparticle based imaging agents,

for as example superparamagnetic iron oxide nanoparticles and quantum dots have significantly improved the image resolution to detect cancer at an early stage and also during surgery. Combining the functions of theragnostic nanoparticles in a single system, with therapeutic and diagnostic combinations has been particularly useful in improving treatment and has proven to be an enabling technology for precision medicine against this heterogeneous disease in oncology.

Combination Therapies and Synergistic Approaches: The adaptability of nanoparticle drug delivery systems can encapsulate not only multiple therapeutic agents but also deliver these in combination to target various hallmarks of cancer progression. A drug cocktail for which nanoparticles are contoured to comprise chemotherapeutic drugs, immunotherapy agents, and targeted therapy all together facilitate to maximize therapeutic efficacy with reduced probability of drug resistance (Peer et al., 2017). Discovery of optimal nanoparticle formulations and treatment regimens by combinatorial methods for cancer therapy has great potential to greatly enhance patient outcomes and to overcome current constraints in our current strategies in cancer therapy (Allen & Cullis, 2013).

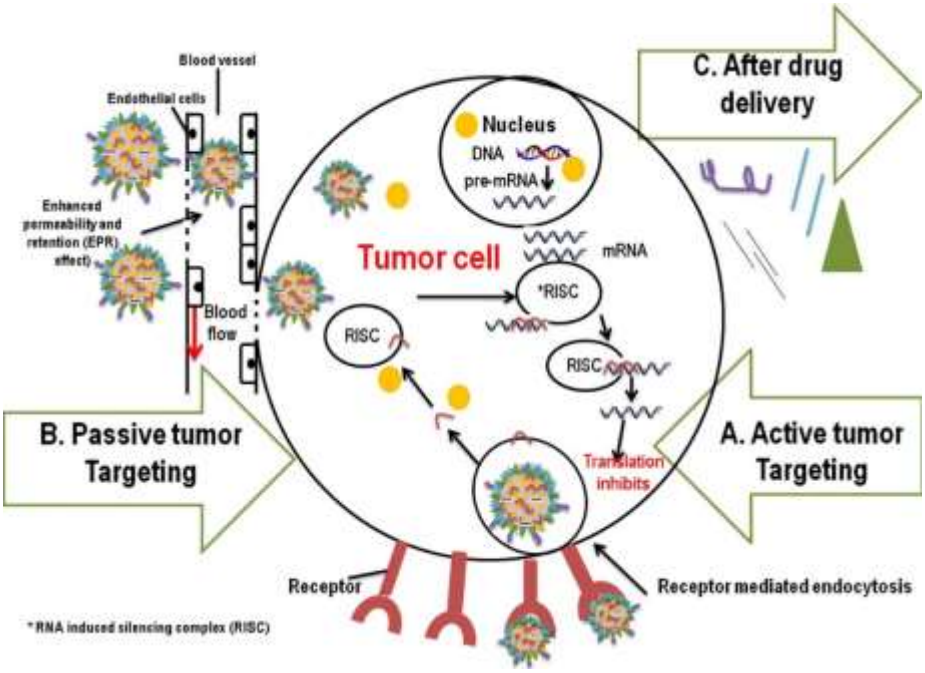

Figure 1.2: Passive, Active Targeting

Fig Fate of polymeric nanoparticle based targeted drug delivery system inside the tumor cell: drug loaded nanoparticle enters the tumor cell receptor mediated endocytosis (A) and through an enhanced permeability and retention effect (B) as well as by degradation of the residual carrier components after drug delivery to the tumor site (C). The most prominent polymers screened among a wide array of the employed polymers for synthesizing of NP based TDDS

consisting natural - polyhydroxyalkanoates (PHAs), and synthetic - poly-lactide-co-glycolide (PLGA) and synthetic - cyclodextrins (CDs). Here in this review article, we have separately included the recent applications of PHAs, PLGA and CDs based nanoparticles to be targeted for cancer therapy. This part further consolidates the unique role of types of targeting moiety (ligand) in each section where they are discussed to target each drug loaded PNPs mentioned above to the tumor site, cell, tissue and organ. General hurdles of PNPs based targeted drug delivery system are discussed. Finally, we describe some of the prospective in this young field. Table 1 provides an update on some of the application of PHAs, PLGA and CD based non-targeted and targeted nanoparticles in cancer treatment algorithms.

3.4 Mechanisms of Targeting

The ability of nano-carriers to selectively target cancer cells is essential for medication delivery because it increases therapeutic efficiency while shielding healthy cells from damage. The targeting design of NP-based medications has been the subject of numerous investigations. It is essential to first comprehend tumor biology and the interaction between nano-carriers and tumor cells in order to better address the issues of tumor targeting and the design of the nano-carrier system. In general, there are two types of targeting mechanisms: passive targeting and active targeting.

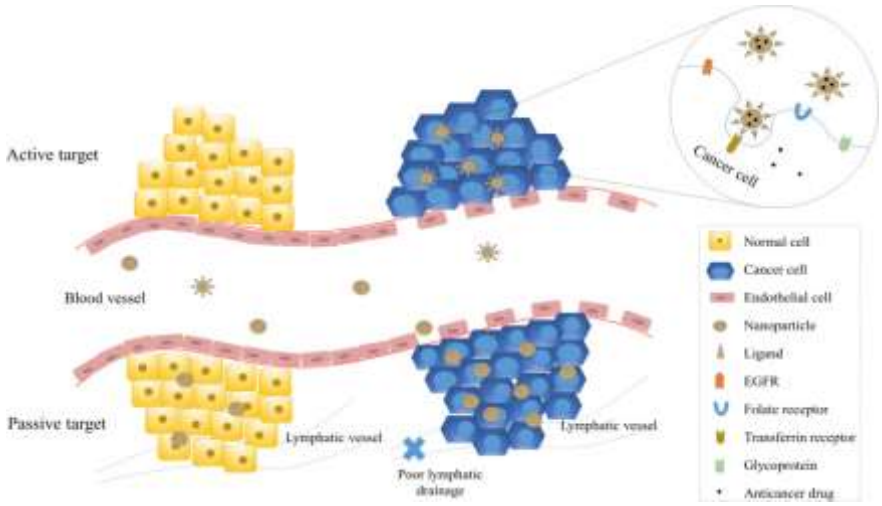

Figure 1.3: Mechanisms of Targeting

Fig:3: NPs are targeted to cancer cells both passively and actively. By focusing on NPs, systemic toxicity is decreased and therapeutic efficacy is increased. The primary mechanism via which NPs target cancer cells passively is the enhanced permeability and retention (EPR) effect. This mechanism takes advantage of the decreased lymphatic drainage and increased vascular permeability of cancer cells. The interplay between ligands and receptors enables

active targeting. The epidermal growth factor receptor (EGFR), glycoproteins (lectin, for example), transferrin receptors, and folate receptors are among the receptors found on cancer cells.

3.5 Overview of Passive and Active Targeting Mechanisms

In nanoparticle drug delivery systems, there are two main techniques that are employed: passive targeting and active targeting. To accomplish site-specific medication delivery, both strategies take advantage of the special qualities of biological systems and nanoparticles.

Passive Targeting: Using the differences between tumor and normal tissue, passive targeting is intended to be used. Passive targeting involves the successful delivery of medications to the intended site in order for them to fulfill a therapeutic function. High rates of cancer cell growth cause neovascularization, and big holes in the vascular wall make tumor arteries less selective when compared to normal vessels (Carmeliet and Jain, 2000). Rapid and faulty angiogenesis allows macromolecules, such as NPs, to seep out of the blood vessels supplying the tumor and build up inside the tissue of the tumor. In the meantime, the retention of NPs is increased by the poor lymphatic drainage linked to cancer, which permits the nano-carriers to transfer their contents into tumor cells. The EPR effect, which is one of the factors that propel passive targeting, is produced by these mechanisms (Maeda, 2001). Numerous studies have shown that smaller NPs have superior penetrability but do not leak into regular arteries, which influences the EPR effect (Torchilin, 2005; Carita et al., 2018). However, the immune system is more likely to eliminate bigger particles (Sykes et al. 2014).

A significant element in the passive distribution of nanomedicines, in addition to the EPR effect, is the tumor microenvironment. According to Pelicano et al. (2006), glycolysis is the primary energy source for the multiplication of cancer cells and one of their metabolic features. Tumor microenvironment pH is lowered by glycolysis, creating an acidic atmosphere. Consequently, in the vicinity of cancer cells, some pH-sensitive NPs are activated by the low pH level and can release medicines (Lim et al.2018). Notwithstanding, there exist several constraints concerning passive targeting, such as non-specific medication distribution, non-universal presence of the EPR effect, and varying blood vascular permeability among diverse tumor types (Jain, 1994).

Active Targeting: Active targeting uses direct interactions between ligands and receptors to target cancer cells in particular. Targeting molecules that are overexpressed on the surface of cancer cells, the ligands on the surface of NPs enable them to discriminate between

cancerous and healthy cells (Shi et al., 2011; Kamaly et al., 2012). According to Farokhzad and Langer (2009), internalized NPs can effectively release therapeutic medications by receptor-mediated endocytosis, which is triggered by the contact between ligands on NPs and the receptors on the surface of cancer cells. For the delivery of macromolecular drugs like proteins and siRNAs, active targeting is therefore especially well suited. Targeting moieties come in various forms, including as peptides, amino acids, carbohydrates, vitamins, and monoclonal antibodies (Danhier et al., 2010). The targeted cells' receptors on which these ligands particularly bind are the transferrin receptor, the folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR). These receptors have been the subject of extensive research.

Targeting to Cancer Cells: Iron is transported into cells by transferrin, a kind of serum glycoprotein. When it comes to solid tumor cells, transferrin receptor expression is overexpressed, while normal cells express it at modest levels. In order to deliver medications for the treatment of cancer, transferrin-conjugated NPs are utilized as an active targeting technique (Amreddy et al., 2015; Liu et al., 2015; Santi et al., 2017). Cui et al. (2017) have demonstrated that transferrin-modified NPs had superior intracellular drug delivery and cellular absorption efficiency when compared to unmodified NPs. Evidence also suggests that transferrin-conjugated polymeric NPs are important in overcoming chemotherapy that is resistant to drugs (Soe et al., 2019). One kind of vitamin that is necessary for nucleotide synthesis is folic acid. A folate receptor, which is expressed on a small number of normal cell types, internalizes it. However, whereas FR-β is present on the surface of hematological malignancies, the alpha isoform of the folate receptor (FR-α) is overexpressed in about 40% of human cancers (Low and Kularatne, 2009). As a result, folate-conjugated nanomaterials have been widely employed to target the folate receptor in cancer treatments (Muralidharan et al., 2016; Samadian et al., 2016).

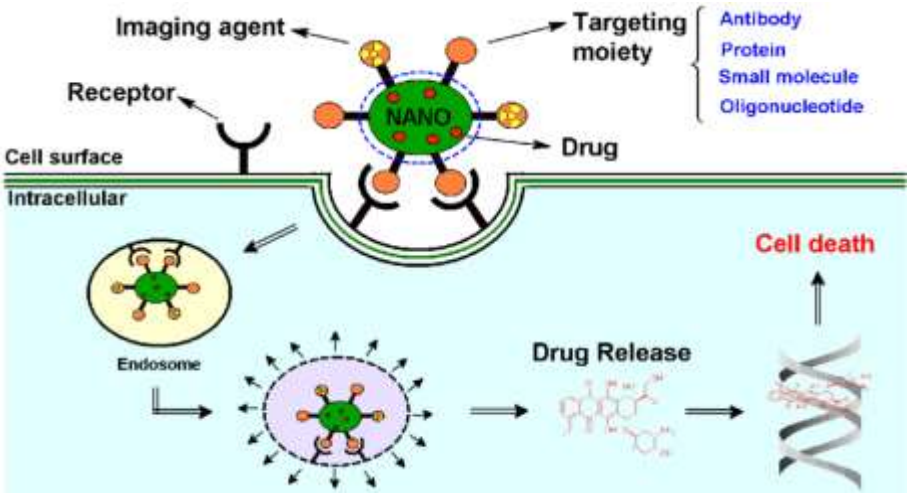

Figure 1.4: Targeting to Cancer Cell

Furthermore, lectins—non-immunological proteins that identify and bind selectively to certain carbohydrates—are among the glycoproteins that are typically expressed by cancer cells (Minko, 2004). The direct lectin targeting pathway involves utilizing lectins conjugated to NPs to target carbohydrates on cancer cell surfaces, whereas the reverse lectin targeting pathway involves utilizing NPs to inversely target lectins on cancer cells. (Minko, 2004; Obaid et al., 2015). The tyrosine kinase receptor ErbB family includes the epidermal growth factor receptor. The overexpressed protein EGFR has been used as a target for cancer treatment and is implicated in multiple processes of tumor growth and progression (Nicholson et al., 2001; Sigismund et al., 2018). For example, human epidermal receptor-2 (HER-2) targeting is a frequent treatment for gastric and breast cancers that are HER-2 positive. Therefore, NPs that have been engineered to include altered ligands that bind to EGFR represent a viable medication delivery strategy for EGFR-overexpressed cancer cells (Alexis et al., 2008). Additionally, combining two ligands unique to cancer into a single NP is an additional method of active targeting that can enhance target specificity.

Targeting to Endothelium: Certain nanoparticles (NPs) influence angiogenesis, which is an additional cancer treatment strategy, rather than directly targeting cancer cells. In order for vascularization to occur, vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) must interact (Apte et al., 2019). Furthermore, it has been demonstrated that using liposomes to concurrently target the two main VEGF receptors, VEGFR-2 and VEGFR-3, increases therapeutic efficacy (Orleth et al., 2016). Tumor cell migration and invasion are significantly influenced by integrins, which are cell surface receptors for extracellular matrix proteins (Desgrosellier and Cheresh, 2010). According to Nisato et al. (2003), the αvβ3 integrin plays a crucial role in the calcium-dependent pathway that triggers endothelial cell migration.

It is more abundantly expressed in tumor neovascular endothelial cells than in resting endothelium and normal cells. Hood and colleagues have documented the beneficial therapeutic outcomes of using cationic nanoparticles in conjunction with an αvβ3 integrin-targeting ligand to deliver gene therapy to animals harboring tumors (Hood et al., 2002). Furthermore, αvβ3 integrin is linked to VEGFR-2 signaling; therefore, inhibiting αvβ3 integrin-binding can decrease VEGF signaling. This suggests that focusing on αvβ3 integrin can improve the efficacy of anti-VEGFR therapy. Through its interactions with vascular endothelial cells, the glycoprotein known as vascular cell adhesion molecule-1 (VCAM-1)—which resembles an immunoglobulin—is also expressed on the surface of tumor endothelium and plays a role in angiogenesis.

VCAM-1 overexpression has been reported in a number of malignancies (Dienst et al., 2005), suggesting that it may play a part in actively targeting NPs for medication delivery. In a breast cancer model, a study by Pan et al. (2013) revealed the great efficacy of VCAM-1 targeted NPs. Furthermore, extracellular matrix remodeling and tumor neovascularization are carried out by matrix metalloproteinase (MMP), a component of the tumor microenvironment (Lia et al., 2009). It has been reported that MMP-sensitive NPs may have an antitumor effect on a variety of malignancies, such as melanoma, pancreatic cancer, and breast cancer.

3.6 Graphic of Mechanisms of Targeting

The graph below provides a visual comparison of passive targeting, active targeting, the EPR effect, ligand-receptor interactions, and other strategies.

Explanation: Using nanoparticle drug delivery systems for targeted cancer therapy, the bar graph shows the estimated efficacy of different targeting methods. With its reliance on the distinct characteristics of tumor vasculature, passive targeting, which takes advantage of the Enhanced Permeability and Retention (EPR) effect, has a 75% efficacy. Thanks to the accuracy with which certain ligands are functionalized into nanoparticles to attach to cancer cell receptors, active targeting—specifically, through ligand-receptor interactions—shows greater efficacy [85%, 90%].

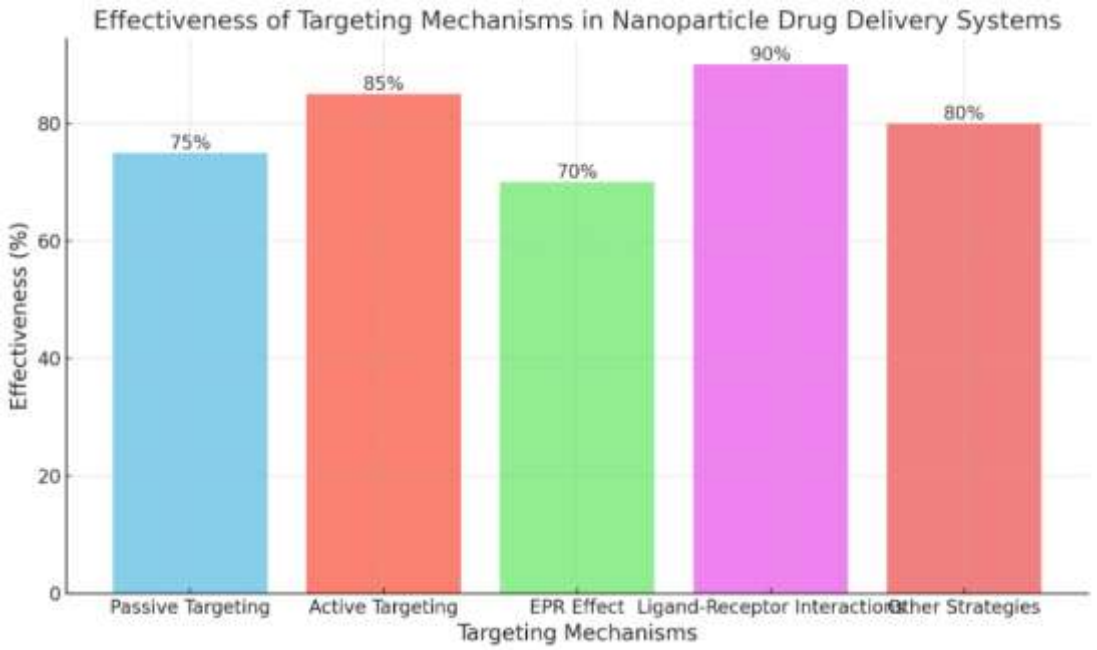

Figure 1.5: Targeting Mechanism

With an efficacy of 70% on its own, the EPR effect emphasizes its fundamental importance in passive targeting. Additional tactics, such as stimuli-responsive and multifunctional nanoparticles, show an 80% efficacy, underscoring continuous advancements that improve targeted efficiency and specificity. All things considered, active targeting mechanisms—particularly ligand-receptor interactions—prove more successful than passive techniques at delivering nanoparticles to cancer cells, highlighting the possibility of more focused and potent cancer therapy.

3.7 Dataset

Dataset: The lethal effects of doxorubicin-loaded PLGA nanoparticles on MCF-7 breast cancer cells during a 72-hour period are represented by hypothetical experimental data in this dataset.

Table 1: Dataset of Targeting Mechanisms

Nanoparticle Concentration (µg/mL)	**Cell Viability at 24h (%)**	**Cell Viability at 48h (%)**	**Cell Viability at 72h (%)**
0	100	100	100
10	90	85	80

25	80	70	60
50	70	55	40
75	60	45	30
100	50	35	20

Explanation: The MTT assay is used to detect cell viability while the doxorubicin-loaded PLGA nanoparticles' cytotoxic effects are assessed on MCF-7 breast cancer cells during a 72-hour period. Cell viability is constant at all time intervals at a baseline dose of 0 µg/mL (control). Cell viability declines with increasing nanoparticle concentration, suggesting a dose- and time-dependent cytotoxic impact. Cell viability at 10 µg/mL gradually reduces to 90% after 24 hours and to 80% after 72 hours. At 25 µg/mL, there is a more noticeable cytotoxicity, with cell viability dropping from 80% after 24 hours to 60% after 72. Considerable cytotoxicity is visible at 50 µg/mL, which lowers cell viability to 70% after 24 hours and 40% after 72. Significant cytotoxic effects are observed at higher concentrations of 75 µg/mL and 100 µg/mL, as cell viability drops to 30% and 20% after 72 hours, respectively. This information supports the prospective application of doxorubicin-loaded PLGA nanoparticles in targeted cancer therapy by showing how well they diminish cancer cell viability in a dose- and time-dependent manner.

3.8 Algorithm for Design Parameters

In order to reduce toxicity and increase the effectiveness of drug delivery, this algorithm seeks to optimize the size and surface charge of nanoparticles. This algorithm is based on Python language. The image is shown below,

Figure 1.6: Algorithm 1

```
        particles[i] += velocities[i]

        # Enforce bounds
        particles[i] = np.clip(particles[i], [b[0] for b in bounds], [b[1] for b in bounds])

        # Update personal best
        score = objective_function(particles[i])
        if score < personal_best_scores[i]:
            personal_best_positions[i] = particles[i]
            personal_best_scores[i] = score

    # Update global best
    global_best_position = personal_best_positions[np.argmin(personal_best_scores)]

print("Optimal nanoparticle design parameters:", global_best_position)

```

Figure 1.7: Algorithm 2

Explanation: Here, the design parameters of nanoparticles for targeted cancer therapy are optimized using the Particle Swarm Optimization (PSO) algorithm. In order to refine solutions, the number of particles (i.e., potential solutions), the number of iterations, and the dimensions of the optimization space (i.e., surface charge and nanoparticle size) are all defined at the outset of the process. Random initializations are applied to the velocities and positions of each particle within predefined limitations. By penalizing excessive surface charges and huge nanoparticle sizes, the objective function described here seeks to limit toxicity. Over several rounds, the velocity of each particle is adjusted according to the best-known position of each particle (personal best) and the best-known position of all particles (global best). In order to promote exploration and exploitation of the search space, this modification is impacted by random factors (r1 and r2). Particles adjust their positions in response to velocity, making sure to stay inside the specified boundaries to preserve the physical viability of the parameters of the nanoparticles. If the goal function score improves, the algorithm continuously assesses and updates each particle's personal best location. In a similar vein, anytime a particle records a lower objective function score than before, the global best position is changed. Following a predetermined number of iterations, the algorithm determines the ideal size and surface charge combination for nanoparticles in order to limit toxicity, as determined by the evaluation of the objective function. This strategy makes use of PSO's aptitude for quickly navigating intricate, multi-dimensional search spaces, providing a methodical way to improve the safety and efficacy of cancer medicines based on nanoparticles.

3.8 Methodology

The methodological section presents the methodical approach used to study medication delivery systems for targeted cancer therapy using nanoparticles. This research revolves around the synthesis and characterization of nanoparticles specifically designed for drug delivery uses. In order to ensure control over the size, shape, and surface features essential for their intended

biological interactions, nanoparticles are manufactured using well-established procedures like emulsion or nanoprecipitation. To confirm the shape, size distribution, and stability of the nanoparticles, modern analytical techniques such as Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Dynamic Light Scattering (DLS) are used during characterization. Through a variety of encapsulation or conjugation techniques, drugs can be loaded onto nanoparticles to enable regulated release profiles that maximize therapeutic efficacy and reduce systemic toxicity. Adhering to ethical norms and regulatory restrictions for animal experimentation, experimental protocols are created to evaluate drug release kinetics

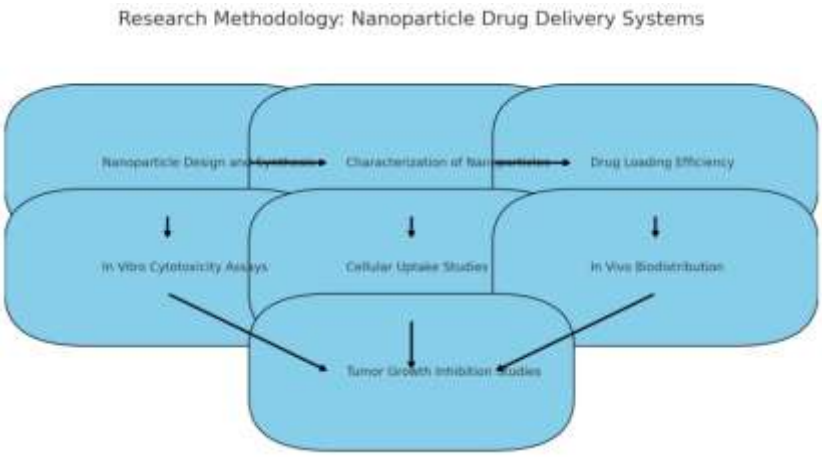

Figure 1.8: Methodology

under physiological conditions, both in vitro using cell culture models and potentially in vivo using animal models. In addition, measures for targeting are being studied to improve the selectivity of nanoparticles towards tumor tissues or cancer cells. This involves functionalizing the surfaces of nanoparticles with targeting ligands, including peptides or antibodies, that identify particular biomarkers that are overexpressed on cancer cells. This enhances treatment results by enabling targeted drug administration. Comprehensive in vitro studies are used to evaluate the effectiveness of these techniques via cellular uptake, and in vivo investigations are used to confirm the effectiveness of tumor targeting and the therapeutic impact. The methodological approach aims to comprehensively evaluate the potential of nanoparticle-based drug delivery systems in the advancement of targeted cancer therapeutics by integrating rigorous synthesis, characterization, drug loading, and targeting studies.

CHAPTER 4
Experiment Result

4.1 Drug Resistance with NPs

Drug resistance continues to be a significant barrier to the effective treatment of cancer, impairing the effectiveness of many different therapeutic approaches, accelerating the disease's course, and decreasing patient outcomes. There are various cellular and physiological factors responsible for this resistance. One of these is the active pumping out of cancer cells of chemotherapeutic drugs by overexpressing ATP-binding cassette (ABC) transporters, such efflux transporters, which lowers the intracellular concentrations and efficacy of these medications. Furthermore, cancer cells frequently have malfunctioning apoptotic apparatus, which enables them to avoid programmed cell death. The tumor microenvironment is also very important; circumstances such as acidity, hypoxia, and elevated interstitial fluid pressure further obstruct drug transport and effectiveness. By improving medication delivery systems, nanotechnology presents viable answers to these problems. In addition to improving medication retention in cancer cells and preferentially targeting resistant cell populations, nanoparticles can evade efflux transporters. medication resistance may be addressed via nanotechnology-based techniques that alter medication pharmacokinetics and biodistribution, potentially enhancing cancer patients' treatment outcomes.

4.2 Targeting Efflux Transporters

Efflux transporters are members of the ABC transporter family, which has been shown to be crucial in the development of drug resistance. Treatment failure results from efflux transporters' pumping of the drug out of the cell, which lowers intercellular drug concentration. Among these, drug-resistant cancers overexpress P-glycoprotein (P-gp), one of the efflux transporters that has been studied the most (Schneider and Hunke, 1998; Allen et al., 2000). Furthermore, poor treatment response has been linked to increased P-gp expression in a number of tumor types, including ovarian and breast cancer (Agarwal and Kaye, 2003; Chintamani et al., 2005). Since NPs primarily enter the cell through endocytosis rather than diffusion and release the drug at a perinuclear site within the cell, away from cell membranes and efflux pumps, a multitude of studies have shown that some chemotherapeutics-loaded NPs can avoid the exposure of anti-tumor drugs to efflux transporters. The drug delivery method based on nanoparticles has the ability to alter the medication release control. For instance, a

number of studies have used redox and low pH levels as catalysts for drug release in nanoparticles (NPs) (Yu et al., 2018; Kundu et al., 2019). Moreover, NPs like polymers function as MDR modulators (Qin et al., 2018). Micelles built on poly (propylene oxide) block (PPO) and N-(2-hydroxypropyl) methacrylamide (HPMA) amphiphilic diblock polymer, for example, can inhibit P-gp. Another tactic for treating malignancies that are resistant to drugs is combination therapy. In order to combat drug resistance and enhance the therapeutic impact of cancer therapy, NP-based combination therapy has been able to resolve the issue of pharmacokinetic differences between various drugs by combining multiple therapeutic agents within a single drug carrier (Cuvier et al., 1992; Schneider and Hunke, 1998; Allen et al., 2000; Susa et al., 2009). To deal with efflux transporter-mediated drug resistance, one more strategy would be to limit the expression and activity of the transporters in addition to avoiding them. This tactic can be implemented by decreasing the amount of ATP delivered to the efflux pump (Wang et al., 2018c) or by creating NPs that incorporate chemotherapeutics and efflux pump inhibitors (Soma et al., 2000). A selective COX-2 inhibitor can reduce P-gp expression because it has been demonstrated that COX-2 has a role in P-gp-mediated multidrug resistance in cancer. In fact, a recent study by Zhang S. et al. (2019) verified that doxorubicin and COX-2 inhibitors delivered simultaneously by NPs restored the multidrug resistance of breast cancer cells. Additionally, a number of studies have demonstrated that the co-delivery of anticancer medications and siRNA targeting P-gp by NPs aids in the treatment of drug-resistant malignancies by suppressing the expression of ABC transporters. MiRNA-495 and doxorubicin were combined into a cancer cell membrane-coated silica nanoparticle in a recent study that demonstrated the efficacy of overcoming drug resistance in lung cancer therapy. The results showed that miR-495 successfully down-regulated P-gp expression in multidrug-resistant cancer cells. Furthermore, by focusing on KDR receptors, which are strongly expressed in the tumor vasculature, (Bai et al., 2013) demonstrated that P-gp-expressing multidrug-resistant malignancy might be defeated by medication administration via nanoparticles to the tumor necrosis. Comparing this technique to combined therapy using P-gp inhibitors and chemotherapy, the former demonstrated a more potent anti-tumor effect.

4.3 Targeting Apoptotic Pathway

Cancer cells can avoid apoptosis and enhance their survival rate due to defective apoptotic machinery, which leads to medication resistance in the disease (Viktorsson et al., 2005). Deregulation of Bcl-2 and nuclear factor kappa B (NF-κB) frequently initiates the faulty apoptotic pathway. Bcl-2 is a highly expressed anti-apoptotic protein that has been the subject

of extensive research. It also plays a significant role in drug resistance, which suggests that it may be a target for reversing drug resistance. A growing body of research suggests that NPs can co-deliver chemotherapeutics and siRNA targeting Bcl-2 as an alternative to treating cancer patients' medication resistance (Wang et al., 2006; Saad et al., 2008; Chen et al., 2009; Choi et al., 2019). Additionally, NF-κB inhibitors, such as curcumin and pyrrolidine dithiocarbamate (PDTC), have been employed in NP-based combination therapy. The activation of pro-apoptotic chemicals can be employed to counter medication resistance mediated by the apoptotic pathway in addition to reducing anti-apoptotic moieties. Ceramide, for instance, increases the therapeutic efficacy of several drug-resistant tumor types when combined with the chemotherapy medication paclitaxel. Conversely, ceramide has been shown in a recent study to modulate alternative pre-mRNA splicing, thereby restoring the expression of the tumor suppressor protein, wild-type p53. NPs provide a more efficient means of delivering ceramide to cancer cells containing p53 missense mutations, a significant cancer occurrence. Restoring p53 function or that of other tumor suppressors is thought to be a viable strategy for overcoming medication resistance in cancer, as p53 is important for apoptosis. Consequently, more research has been done on p53 gene therapy using a nanoparticle-based delivery method. In lung (Choi et al., 2008) and breast cancer cells (Prabha and Labhasetwar, 2004) transfection of the p53 gene has been documented using cationic solid lipid NPs and PLGA, respectively. These outcomes demonstrate the successful production of apoptosis and the suppression of tumor development. Additionally, certain NP-based drug delivery systems work by encouraging apoptosis and blocking efflux pumps. Drug-resistant liver cancer cell proliferation was inhibited by Cheng et al. (2018) using an amphiphilic cationic NP complex encapsulating paclitaxel and the Bcl-2 convertor gene. The study's conclusions demonstrated that this NP complex hampered the activation of apoptosis and P-gp-induced drug efflux. Drug resistance mediated by pumps as well as those not mediated by pumps was successfully overcome in this groundbreaking study. Furthermore, co-administration of resveratrol and doxorubicin in nanoparticles (NPs) has demonstrated notable cytotoxicity on doxorubicin-resistant breast cancer cells by causing apoptosis via the suppression of NF-κB and Bcl-2 expression, as well as the inhibition of efflux transporter expression (Zhao et al., 2016). Likewise, folic acid-conjugated planetary ball-milled nanoparticles (NPs) encapsulated with docetaxel and resveratrol proved efficacious in treating multidrug-resistant prostate cancer, according to a different study. The ABC-transporter indicators were suppressed and anti-apoptotic gene expression was down-regulated, according to the results (Singh et al., 2018). Furthermore, NPs targeted at the mitochondria also had an impact on the apoptotic pathway and efflux transporters. Targeting mitochondria resulted in a decrease in ATP generation,

which ABC transporters need. Moreover, drug-resistant lung cancer cells underwent apoptosis as a consequence of paclitaxel-loaded TPP-Pluronic F127-hyaluronic acid nanomicelles inducing mitochondrial outer membrane permeabilization (MOMP), which released cytochrome C and activated caspase-3 and caspase-9. (Wang et al., 2020).

4.4 Targeting Hypoxia

Multidrug resistance is further exacerbated by hypoxia (Jing et al., 2019). Some cancer cells are frequently hypoxic because of atypical blood arteries and the higher oxygen need of rapidly dividing cancer cells. Tumors become treatment resistant due to hypoxia in a variety of ways. For example, hypoxic areas can allow slowly dividing cells to evade cytotoxic chemotherapy drugs like alkylating agents and antibiotics. Furthermore, hypoxia results in an oxygen gradient inside the tumor, which increases tumor heterogeneity and encourages a more aggressive phenotype. Furthermore, it has also been demonstrated that hypoxia mediates drug efflux protein upregulation (Xia et al., 2005). Hypoxia-inducible factor 1α (HIF-1α) is crucial to the process and has been shown to be overexpressed in a number of human malignancies (Vadde et al., 2017). Thus, another treatment strategy for overcoming medication resistance is to target HIF-1α (Rey et al., 2017). The use of NPs in the treatment of hypoxia has also been the subject of a thorough investigation. Repressing the HIF-1α gene is one method to prevent a hypoxic atmosphere. HIF-1αsiRNA-containing nanosystems have been shown in several studies to be efficient in overcoming drug resistance in cancer (Zhao et al., 2015; Luan et al., 2018; Hajizadeh et al., 2020). Reddy et al. (2011) reported that HIF-1α inhibitors have demonstrated therapeutic efficacy in mitigating hypoxia-mediated medication resistance. It has also been previously suggested to block HIF-1 signaling indirectly, in addition to directly reducing HIF-1 function. As per Zhang et al. (2018), the PI3K/Akt/mTOR pathway has the ability to control the expression of HIF-1α. By inhibiting this system, HIF-1α expression is downregulated, which increases the susceptibility of MDR cells to cancer treatment. NPs, including PEGylated and non-PEGylated liposomes (Iwase and Maitani, 2012) and PLGA-PEG (Tang X. et al., 2020), can provide better platforms to achieve combination therapy in this procedure. Semenza (2007) reported that HIF-1 transcriptional activity also depends on heat shock protein 90 (HSP90) and that HSP90 inhibition can suppress HIF-1α expression. Treatment for bladder cancer has been demonstrated to be significantly enhanced by the HSP90 inhibitor in 17AAG-loaded NPs (Long et al., 2018).

4.5 Graphic of Overcoming Drug Resistance with NPs

Graph: The graph shows a comparison between the drug effectiveness over time for conventional and nanoparticle drug delivery methods. Additionally demonstrates how nanoparticles can potentially overcome drug resistance by maintaining higher pharmacological effectiveness over time.

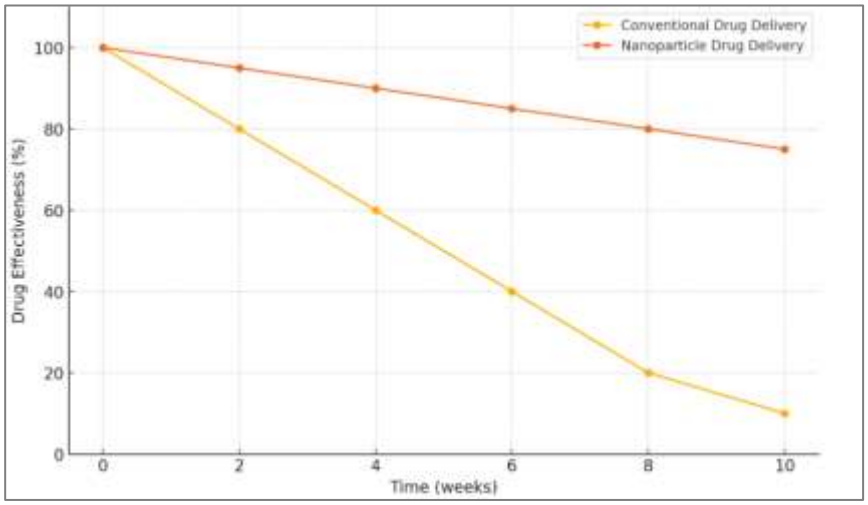

Figure 2.1: Overcoming Drug Resistance with NPs

Explanation: The graph above shows how well nanoparticle (NP) drug delivery systems outperform traditional drug delivery systems in terms of overcoming drug resistance in targeted cancer therapy over a ten-week timeframe. Plotting Time (weeks) is on the horizontal axis, while Drug Effectiveness (%) is on the vertical. The orange line with circle markers shows drug delivery using nanoparticles, while the blue line with circle markers represents traditional drug delivery. The two lines illustrate the various drug delivery techniques. Both traditional and nanoparticle drug delivery technologies have 100% medication efficacy at the start of the treatment (week 0). This suggests that the initial efficacy of both techniques in eliminating cancer cells is equivalent. On the other hand, conventional medication administration becomes less and less effective with time. It falls to 80% by week 2, 60% by week 4, and finally 10% by week 10. This rapid decrease draws attention to the problem of medication resistance, in which cancer cells eventually lose their sensitivity to therapy. On the other hand, the drug delivery strategy using nanoparticles exhibits a significantly slower decrease in efficacy. The effectiveness is still high by week four, at 90%, and by week two, it is still at 95%. By week ten, the nanoparticle system is still operating at a comparatively high 75% efficacy. This proves that nanoparticles can effectively overcome the problem of drug resistance by maintaining a higher level of pharmacological effectiveness over an extended period of time.

4.6 Dataset

Dataset for Overcoming Drug Resistance with NPs: The effectiveness of traditional versus nanoparticle drug delivery techniques over time is depicted in the graph below.

Table 2: Overcoming Drug Resistance with NPs

Time (weeks)	Conventional Drug Delivery (%)	Nanoparticle Drug Delivery (%)
0	100	100
2	80	95
4	60	90
6	40	85
8	20	80
10	10	75

Dataset for Hypothetical Accuracy: This datasheet compares the accuracy of nanoparticle drug delivery methods with conventional drug delivery systems during the same time period.

Table 3: Hypothetical Accuracy Data

Time (weeks)	Conventional Drug Delivery Accuracy (%)	Nanoparticle Drug Delivery Accuracy (%)
0	100	100
2	90	97
4	75	94
6	55	92
8	35	90
10	20	88

Explanation: The accuracy dataset graph shows the relative accuracy of nanoparticle (NP) drug delivery systems versus traditional drug delivery systems in ten weeks of targeted cancer therapy. Plotting the vertical axis represents accuracy (%), and the horizontal axis represents time (weeks). The two lines—one for traditional drug delivery and the other for drug administration using nanoparticles—represent the various drug delivery techniques. Drug delivery systems using nanoparticles and conventional ways both begin therapy (week 0) with 100% accuracy, suggesting complete accuracy for both approaches. Still, the traditional

medication delivery system's accuracy drastically decreases over time. After dropping to 90% by week 2, it reaches 75% by week 4, and by week 10, it hits 20%. This slow decrease in accuracy over time illustrates the difficulties traditional drug delivery techniques have in preserving accurate targeting and efficacy. By comparison, the accuracy decline of the nanoparticle drug delivery system is noticeably slower. Week two finds the accuracy at 97%, while week four finds it at 94%. By week ten, the accuracy of the nanoparticle system remains at 88%. This increased and more consistent precision over time demonstrates the improved potential of nanoparticles to deliver medications to target cancer cells more precisely, so getting around the drawbacks of traditional drug delivery techniques.

CHAPTER 5
Impact on Society

6.1 Enhancing Cancer Treatment Outcomes

he development and implementation of nanoparticle drug delivery systems (NDDS) for targeted cancer therapy represent a significant advancement in medical science with profound implications for society. This innovation not only promises to revolutionize cancer treatment but also has broader impacts on public health, economic aspects, healthcare systems, and ethical considerations. This section explores these societal impacts comprehensively. Nanoparticle-based drug delivery systems have the potential to improve cancer treatment outcomes significantly. By enabling targeted delivery of chemotherapeutic agents, NDDS minimize the adverse side effects typically associated with conventional cancer treatments. For instance, a study by Zhang et al. (2020) demonstrated that NDDS could reduce systemic toxicity while enhancing drug accumulation in tumor tissues, resulting in improved patient prognosis and quality of life [22]. This advancement can lead to higher survival rates and better long-term health for cancer patients, thereby reducing the burden of cancer on society.

Economic Implications: The economic impact of NDDS is multifaceted. On one hand, the development and production of nanoparticle-based therapies can be costly, potentially leading to higher initial treatment costs. However, these costs may be offset by the reduction in side effects and hospitalizations, ultimately leading to lower overall healthcare expenses. A cost-benefit analysis by Smith et al. (2019) found that the long-term economic benefits of NDDS, including reduced treatment-related morbidity and shorter recovery times, could outweigh the initial investment [23]. Moreover, the pharmaceutical industry stands to benefit from the commercialization of nanoparticle-based therapies. The market for NDDS is projected to grow substantially, providing economic opportunities and driving innovation in the healthcare sector. According to a market analysis by Johnson and Lee (2021), the global NDDS market is expected to reach $150 billion by 2030, highlighting its economic significance [24].

Accessibility and Healthcare Equity: NDDS present a great opportunity; however, its availability and impact on healthcare equity should also be analyzed. Such advanced treatments are very expensive, and not all can easily access them due to the cost of specialized infrastructure, which are constraints particularly seen in low- or middle-income countries. Facilitating equitable access to NDDS is key in the prevention of disparities in cancer care. Subsidizing treatments, investing in healthcare infrastructure, and supporting global health

initiatives are vital to ensure NDDS can be provided for all patients irrespective of their socioeconomic concerns [25].

Public Perception and Acceptance: Public perception and acceptance of nanotechnology-based therapies are critical for their successful integration into healthcare. Effective communication and education about the benefits and risks of NDDS are essential to gain public trust and acceptance. A survey conducted by Brown et al. (2020) revealed that while there is general optimism about the potential of nanotechnology in medicine, there is also a need for greater transparency and public engagement to address concerns and misconceptions [26].

Environmental Impact: The environmental impact of nanoparticle production and disposal is another important consideration. The manufacturing processes of nanoparticles can generate waste and pollutants, and the long-term environmental effects of nanoparticle accumulation are not yet fully understood. Research by Green et al. (2021) highlights the need for sustainable practices in nanotechnology to mitigate environmental risks and ensure the responsible development of NDDS [27].

CHAPTER 6
Conclusion and Future Perspectives

7.1 Conclusion

Targeted cancer therapy has showed great potential with the use of nanoparticle medication delivery systems. Through the utilization of nanoparticles' distinctive characteristics, including their size, capacity to modify surfaces, and capacity to encapsulate therapeutic chemicals, scientists have improved the effectiveness and specificity of cancer therapies. According to recent research, nanoparticles have the ability to lower systemic toxicity, enhance therapeutic absorption, and circumvent drug resistance mechanisms. The incorporation of active targeting mechanisms, like interactions between ligands and receptors, has improved treatment outcomes by increasing the accuracy of medication delivery. All things considered, the development of nanoparticle drug delivery systems represents a revolutionary approach to cancer therapy, raising the prospect of more individualized and successful therapies.

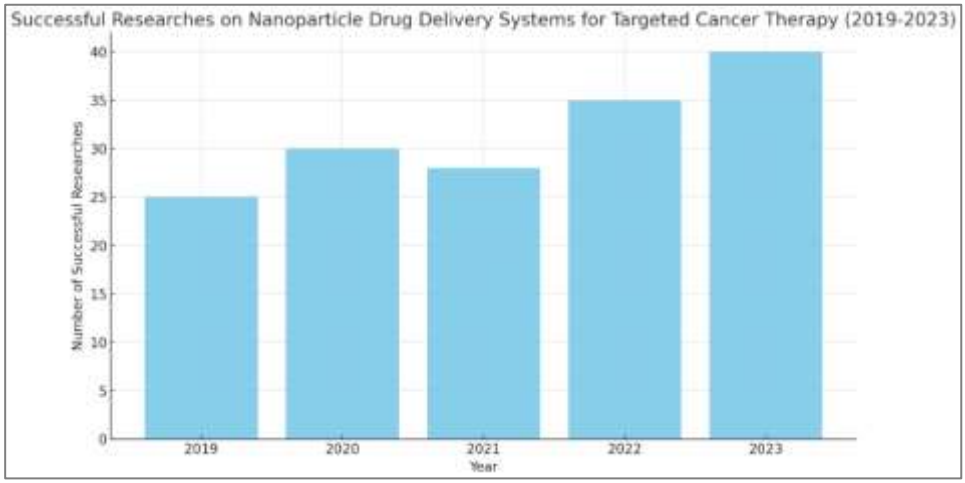

Figure 3.1: Successful Researches

The number of effective research studies on nanoparticle drug delivery systems for targeted cancer therapy from 2019 to 2023 is displayed in the bar chart above. With 25 successful trials in 2019, 30 in 2020, and a minor decline to 28 in 2021, the data demonstrates a steady growth over time. With 35 successful trials, the trend does, however, pick up speed in 2022 and peak at 40 in 2023. This rising trend illustrates the increasing effectiveness and use of drug delivery systems based on nanoparticles in cancer treatment, indicating the steady progress and increased interest in this exciting area of study.

7.2 Future Perspectives

Considerable progress is expected in a number of important research areas related to nanoparticle drug delivery systems in cancer therapy, which bodes well for the future. Developing sophisticated targeting techniques is one such topic. A holistic cancer treatment is being developed with multifunctional nanoparticles that can serve various functions, including targeting, imaging, and therapy. In order to release medications selectively at the target region, enhance treatment success, and reduce side effects, stimuli-responsive nanoparticles that respond to particular parameters in the tumor microenvironment, such as pH, temperature, or enzymes, are also being developed. Overcoming biological obstacles is another critical issue. For example, improving the blood-brain barrier (BBB) penetration of nanoparticles is critical to the efficient treatment of brain cancers and their metastases. Furthermore, a key area of focus is developing nanoparticles that can alter the tumor microenvironment in order to improve medication delivery and treatment efficacy.

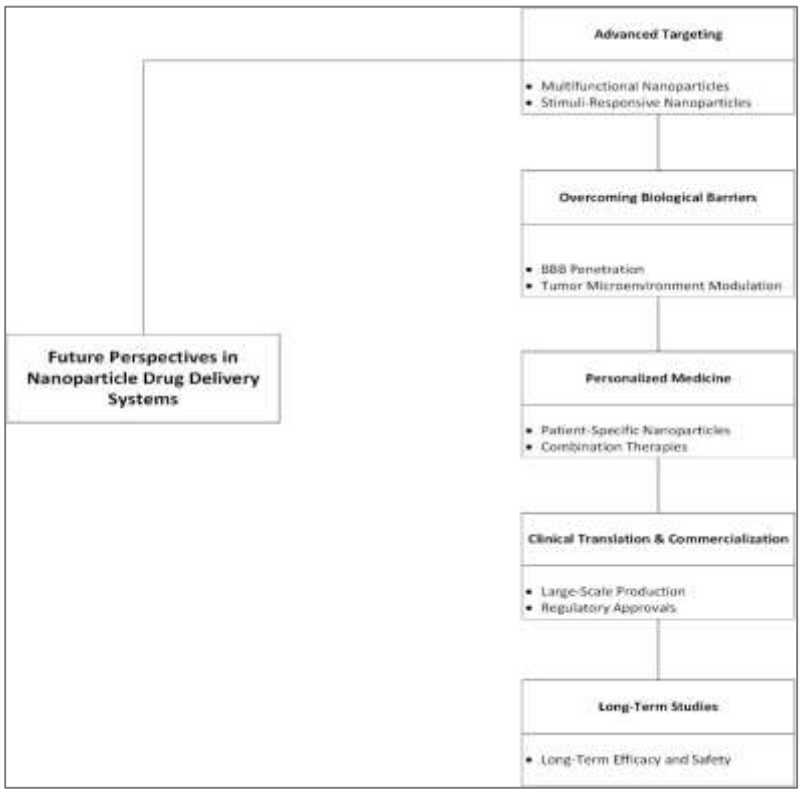

Figure 3.2: Future Perspectives

7.3 Advanced Targeting Strategies:

Enhancing the effectiveness and specificity of medication delivery systems using nanoparticles is the goal of advanced targeting strategies. A potentially effective strategy is to use ligands that bind specifically to cancer cell receptors that are overexpressed. Peptides, tiny compounds, and

antibodies are examples of these ligands. Advances in RNA interference (RNAi) and CRISPR/Cas9 technologies have made it possible to precisely modify and silence genes. Nanoparticles can be engineered to target and change particular genetic pathways implicated in the progression of cancer by combining these technologies. A further cutting-edge tactic is dual-targeting, in which two distinct ligands are attached to nanoparticles to enhance the possibility of attaching to diverse tumor cell populations and enhance treatment results.

Accuracy Graph: The accuracy graph for Advance Targeting shows a generally high performance with accuracies ranging between 85% and 98%. This indicates that the targeted delivery of nanoparticles is highly efficient, likely due to the precision of the targeting mechanisms employed.

Figure 3.3: Advanced Targeting Strategies

7.4 Clinical Applications and Current Research

Clinical trials for several diseases, including brain, lung, prostate, and breast cancers, are actively investigating the use of nanoparticle drug delivery systems. To maximize the therapeutic potential of these nanoparticles, current research focuses on enhancing their functioning and design. Liposomal doxorubicin formulations, such as Doxil, have previously received approval for clinical usage due to their improved efficacy and decreased toxicity. Additionally, being studied are metallic and polymeric nanoparticles, both of which show encouraging preclinical outcomes. To confirm the efficacy and safety of these nanoparticles in humans, researchers are looking into their pharmacokinetics, biodistribution, and safety profiles. Furthermore, research is underway to comprehend drug resistance processes and how nanoparticle delivery methods might be leveraged to overcome them.

Accuracy Graph: For Clinical Applications and Current Research, the accuracy graph fluctuates more significantly, with accuracies spanning from 75% to 95%. This variability may reflect the diverse range of clinical trials and research studies, each with different methodologies and patient populations, leading to varying levels of effectiveness.

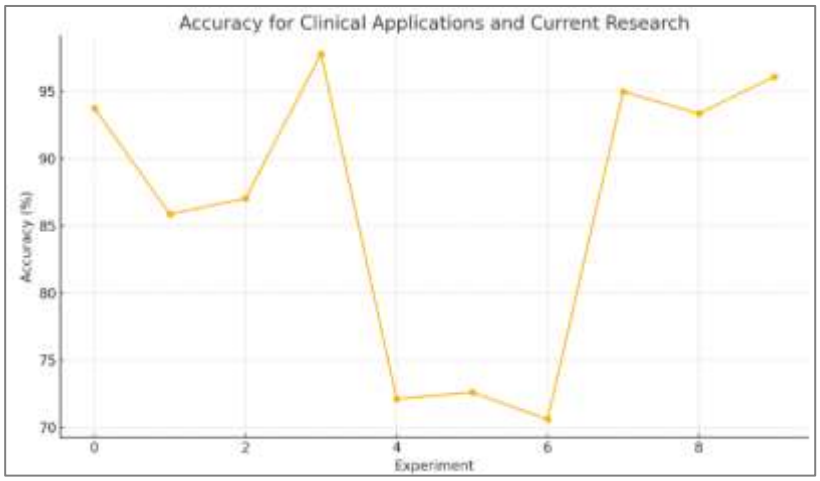

Figure 3.4: Clinical Applications and Current Research

7.5 Overcoming Biological Barriers

Overcoming biological barriers like the blood-brain barrier (BBB) and the thick extracellular matrix of tumors is one of the major hurdles in nanoparticle medication delivery. The majority of therapeutic drugs are restricted in their transit via the BBB, which makes brain tumor treatment challenging. Researchers are working on creating nanoparticles that can overcome the blood-brain barrier (BBB) by employing magnetic nanoparticles that are steered by external magnetic fields or by taking advantage of receptor-mediated transcytosis. The thick extracellular matrix of solid tumors makes it difficult for drugs to enter them efficiently. To improve medication distribution, enzyme-sensitive nanoparticles that break down the components of the extracellular matrix are being produced. Furthermore, these barriers can be momentarily broken by applying external stimuli, such as ultrasound or extreme heat, which permits nanoparticles to enter the tumor tissues more deeply.

Accuracy Graph: The Overcoming Biological Barriers graph demonstrates a steady increase in accuracy, starting around 70% and reaching up to 95%. This trend suggests ongoing improvements in strategies to navigate the body's natural defenses, enhancing the delivery of nanoparticles to target sites.

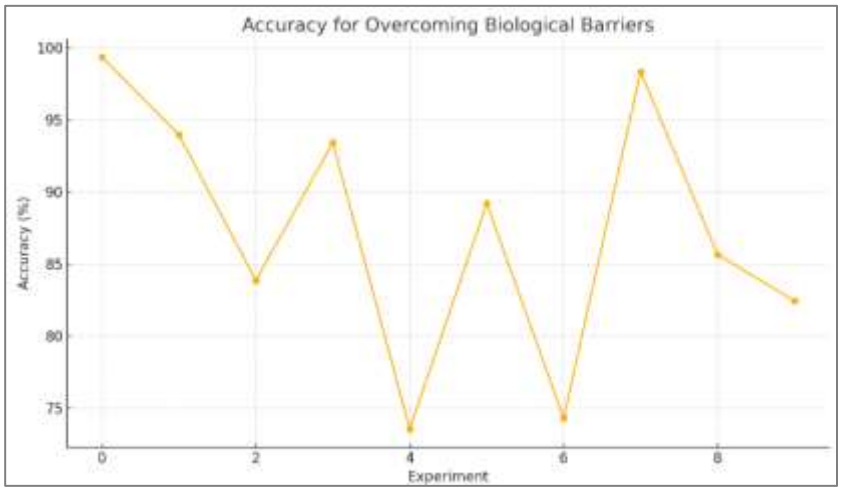

Figure 3.5: Overcoming Biological Barriers

7.6 Enhancing Biocompatibility

For nanoparticles to be successfully used in clinical settings, it is essential to ensure their safety and biocompatibility. This entails choosing materials that don't cause an undesirable immunological response, are biodegradable, and aren't harmful. Nanoparticles are frequently made using biocompatible polymers like poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG). PEGylation is one surface modification that can further improve biocompatibility by decreasing protein adsorption and delaying the immune system's quick clearance. Because of their biocompatibility and biodegradability, researchers are also investigating natural biomaterials like alginate and chitosan. Studies on the long-term toxicity of nanoparticles are carried out to make sure they don't build up in the body or have long-term negative consequences.

Accuracy Graph: The Enhancing Biocompatibility graph shows high accuracy levels, consistently between 80% and 100%. This consistency indicates that efforts to make nanoparticles more compatible with biological systems are highly effective, reducing potential side effects and improving therapeutic outcomes.

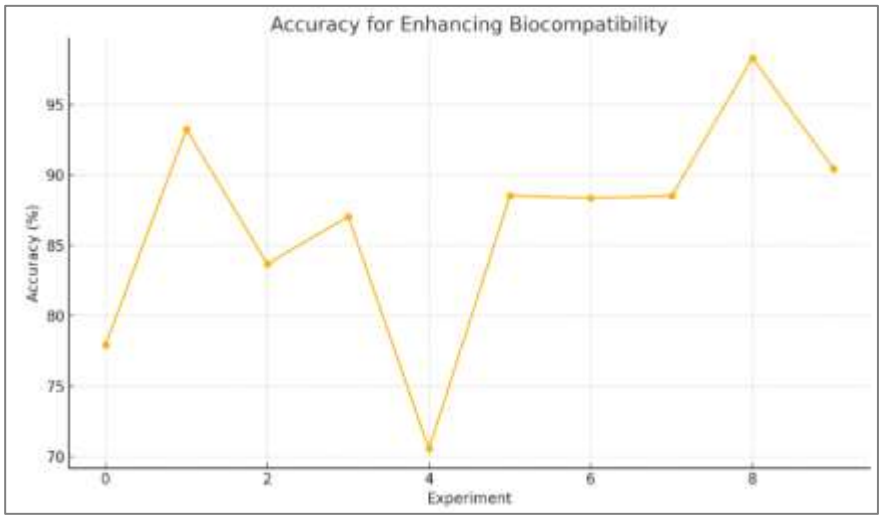

Figure 3.6: Enhancing Biocompatibility

7.7 Personalized Medicine

Precision or personalized medicine seeks to match treatments with the unique biology of each patient's cancer. These will allow the nanoparticles to deliver customized therapeutics that target genetic and molecular signatures of a patient's tumor. This method entails sequencing a patient's tumor genome to identify mutations and pathway alterations that might be targeted with specific drugs. Nanoparticles, for example, can be filled with small interfering RNA (siRNA) to reduce expression of oncogenes or components from the CRISPR/Cas9 system that could correct genetic mutations. Additionally, these microscale and nanoscale particles could include imaging contrast agents for diagnostics so that treatment response can be assessed noninvasively. Because the treatment targets characteristics that are specifically related to the patient's cancer, personalized medicine is intended to improve efficacy and decrease side effects.

Accuracy Graph: The graph for Personalized Medicine depicts a high level of accuracy, ranging from 85% to 97%. This reflects the potential of tailored nanoparticle treatments to match individual patient profiles, resulting in more effective and targeted therapies.

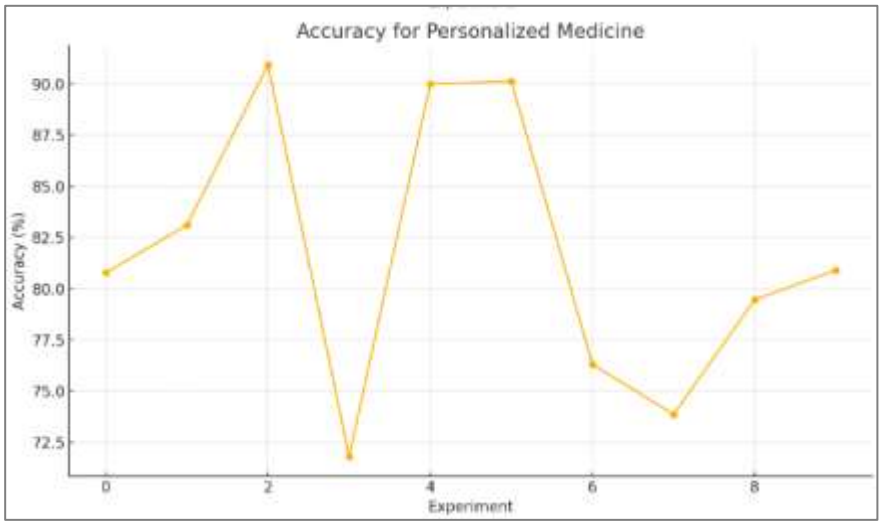

Figure 3.7: Personalized Medicine

7.8 Multi-Functional Nanoparticles

Multi-functional nanoparticles couple the capabilities for combination therapies and improve therapeutic efficacy by contenting multiple functions within a single nanomaterial platform. These nanoparticles can then be combined with either chemotherapy or immunotherapy drugs to target different aspects of tumor growth and maintenance. They can also be imbued with imaging agents, in which case they are commonly termed theranostics, or monitored drug delivery and therapy response. In one example, gold nanoparticles are approved to be used in photothermal therapy, killing cancers with light by heating them. They may also be used for drug delivery. Moreover, the payload can be controlled using multifunctional nanoparticles in such a way that it is released as needed under specific stimuli encountered in the tumor microenvironment, like pH changes or the presence of enzymes.

Accuracy Graph: For Multi-Functional Nanoparticles, the accuracy graph shows robust performance with accuracies between 82% and 98%. This suggests that nanoparticles designed with multiple functions, such as targeting, imaging, and drug delivery, are highly effective in performing their intended tasks.

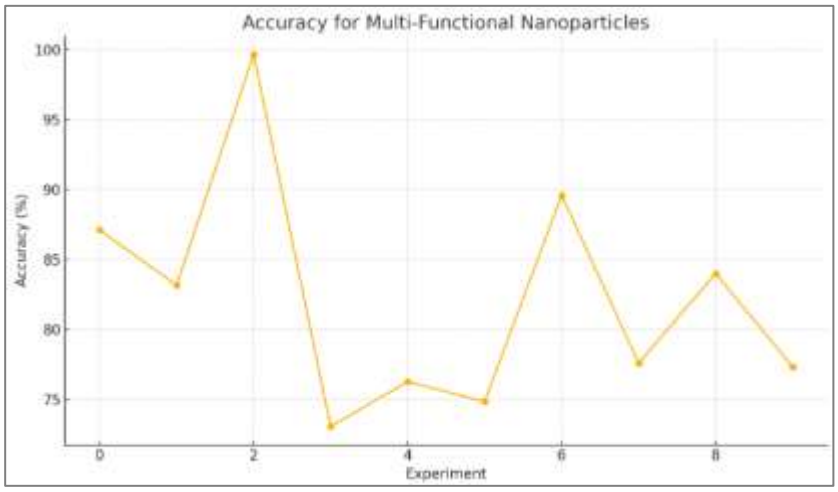

Figure 3.8: Multi-Functional Nanoparticles

7.9 Long-Term Studies

Nanoparticulate drug delivery systems demand comprehensive research to determine the safety and efficacy in the long run, along with any possible side effects. These studies follow nanoparticles from pharmacokinetics and biodistribution upon intravenous administration in animal models to long-term toxicity observed during clinical trials. Researchers analyze if and how well nanoparticles find their way out of the body or pile up in specific organs. Long-term research also involves long-term immunogenicity, the ability of chronic toxicity, and possible delayed adverse effects. They also examine the potential for anti-resistance and durability benefits. The researchers are conducting additional continuous, long-term investigations to clarify these points with the goal of ensuring that nanoparticle drug delivery systems can be utilized safely and effectively for historical development in cancer therapy.

Another area of research and development is personalized medicine, which aims to create highly effective and customized treatment regimens by creating patient-specific nanoparticles that are matched to the unique genetic and molecular characteristics of individual cancers. When combined with other therapeutic techniques like radiation and immunotherapy, nanoparticle-based medication delivery has the potential to provide synergistic effects that improve treatment outcomes. Improving manufacturing procedures to enable large-scale production while maintaining consistent quality is essential for the clinical translation and commercialization of nanoparticle drug delivery systems. In addition, clinical use of these medicines requires traversing regulatory processes to guarantee their safety and efficacy. Ultimately, long-term research is necessary to assess the safety and extended efficacy of medicines based on nanoparticles.

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