Chapter 1

1.1 Background

Controlled drug delivery systems are sophisticated therapeutic approaches designed to release pharmaceutical agents in a regulated manner. Traditional drug administration often results in rapid release and subsequent decline in drug concentrations, leading to fluctuations in therapeutic effectiveness. In contrast, controlled drug delivery aims to maintain drug levels within a desired therapeutic range over extended periods. This methodology enhances treatment efficacy, minimizes adverse effects, and improves patient compliance.

The primary advantage of controlled drug delivery lies in its ability to tailor drug release profiles according to individual patient needs. This capability is particularly significant in the management of chronic diseases, where consistent drug levels are crucial for optimal treatment outcomes. By utilizing a variety of materials and techniques, these systems can modulate both the rate and duration of drug release, ensuring that therapeutic agents effectively reach their targets.[1]

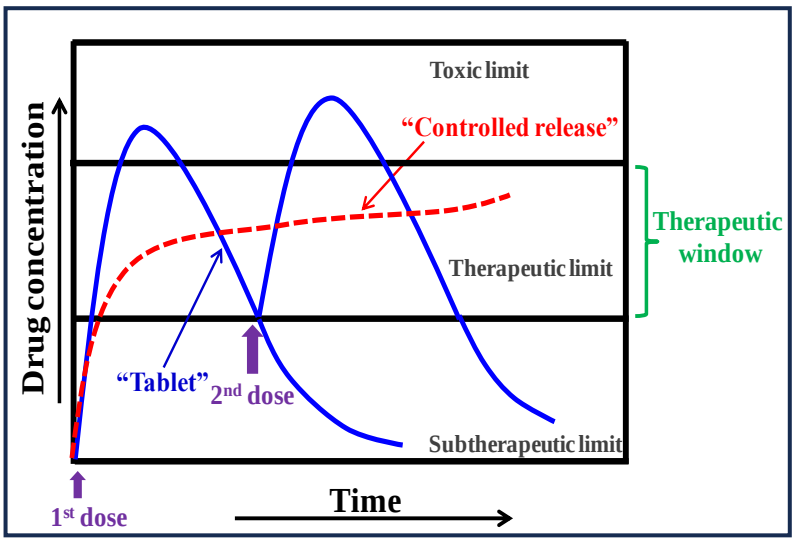

Figure 1.1: A Schematic representations of controlled drug delivery system over conventional one [Bajpai et al., 2008]

Figure 1.1 illustrates the relationship between drug concentration in plasma and the desired time of action. The absorption process of a drug involves several phases. Initially, there is an "ineffective level," where the drug concentration is too low to elicit the desired therapeutic effect. Following this is the "therapeutic level," where the drug concentration is sufficient to provide its intended action. Lastly, the "toxic level" is reached when the concentration becomes potentially harmful to the patient.

In traditional drug delivery systems, such as injections, the drug concentration starts at the ineffective level, ascends to the therapeutic range, and may surpass this level, reaching the toxic threshold. Eventually, the concentration declines back to the ineffective range, requiring multiple doses to sustain therapeutic levels. Conversely, controlled drug delivery systems allow for a steady and predictable release of the drug, maintaining concentrations within the therapeutic range for an extended duration with a single dose. This represents a significant advantage over conventional methods [2].The important advantages of controlled drug delivery systems are …

1) Stable Drug Concentration: Controlled drug delivery systems maintain a consistent concentration of the drug in the bloodstream, leading to minimal fluctuations and enhanced therapeutic effectiveness.

2) Predictable Release Profiles: These systems offer a reliable and predictable release rate over extended periods, ensuring that the drug is available to the body when needed.

3) Reduced Need for Readministration: By providing sustained release, controlled delivery minimizes the frequency of dosing, thereby decreasing the risk of side effects associated with multiple administrations.

4) Protection of Sensitive Therapeutics: Controlled drug delivery can safeguard therapeutic agents with short half-lives, extending their effectiveness and ensuring proper therapeutic action.

5) Enhanced Optimization of Drug Therapy: These systems allow for better optimization of drug regimens, leading to improved patient compliance and overall treatment outcomes.

6) Addressing Drug Solubility Issues: Controlled drug delivery technologies can resolve solubility challenges, thereby reducing drug wastage and maximizing the therapeutic potential of medications [3, 4].

1.2 Different mechanisms of controlled drug release:

Controlled drug release is essential in modern pharmacotherapy, employing several mechanisms to achieve it.

1.2.1 Diffusion controlled release

Diffusion-controlled release involves drug molecules moving from an area of higher concentration within the delivery system to a lower concentration outside, governed by Fick's laws of diffusion. Typically, the drug is dispersed in a polymeric matrix, and factors such as drug size, medium viscosity, and polymer characteristics influence the release rate.

For instance, poly (lactic-co-glycolic acid) (PLGA) nanoparticles are widely studied for their sustained release profiles [5].

1.2.2 Stimuli controlled release

Stimuli-controlled release refers to systems that release drugs in response to specific external or internal stimuli, such as pH, temperature, or biological factors. pH-sensitive nanoparticles, for example, can remain intact in neutral environments but release their drug load in acidic conditions, making them valuable for targeted therapies [6].

1.2.3 Degradation controlled release

Degradation-controlled release involves the gradual breakdown of the drug delivery system, allowing drug molecules to escape. This is particularly relevant for biodegradable polymers, which can be designed to degrade at specific rates based on their chemical composition, enhancing therapeutic applications [7].

1.2.4 Solvent controlled release

Solvent-controlled release occurs when solvent penetration influences drug release. In hydrogel systems, solvent absorption leads to swelling, creating larger pathways for drug diffusion. For instance, hydrogels based on polyvinyl alcohol (PVA) can swell in aqueous environments, facilitating controlled drug release [8].

Each of these mechanisms - diffusion-controlled, stimuli-controlled, degradation-controlled, and solvent-controlled release - plays a crucial role in developing advanced drug delivery systems, aiming to enhance therapeutic efficacy while minimizing side effects.

1.3 Drug Delivery Systems

So far different systems has been formulated for cell specific drug delivery to enhance the potency of chemotherapeutic by reducing its adverse effects. The carriers generally employed hydrogels, dendrimers, micelles, liposomes, nanoparticles, polymer matrix and polymer nanocomposites (Figure **1.2**).

1.3.1 Liposomes

Liposomes have emerged as innovative nanoscale carriers in the realm of controlled drug delivery, offering a multitude of advantages that enhance therapeutic efficacy. Composed of phospholipid bilayers, liposomes can encapsulate a diverse range of therapeutic agents, including both hydrophilic and hydrophobic drugs, thereby addressing solubility challenges that often hinder drug bioavailability. Their biocompatibility and ability to mimic cellular membranes make liposomes particularly suitable for drug delivery applications, minimizing systemic toxicity while maximizing therapeutic effects [9]. One of the key features of liposomes is their capacity for sustained release. By fine-tuning the lipid

composition and surface characteristics, researchers can engineer liposomes for specific targeting of tissues or cells. This targeted delivery is crucial in conditions such as cancer, where selective drug accumulation in tumor cells can significantly enhance treatment outcomes while reducing side effects [10].Moreover, liposomes can be modified with ligands that recognize and bind to specific receptors, further improving their selectivity. In addition to passive targeting, stimuli-responsive liposomes are an exciting development in controlled drug delivery. These liposomes can release their cargo in response to specific environmental triggers, such as changes in pH, temperature, or the presence of certain enzymes [11].This capability allows for a more precise delivery of therapeutics at the desired location and time, thus enhancing the overall treatment regimen. Overall, liposomes represent a promising and versatile approach in the development of advanced drug delivery systems. Their ability to improve drug solubility, achieve targeted delivery, and enable controlled release underscores their potential in enhancing therapeutic outcomes across various diseases, paving the way for more effective and patient-friendly treatment options.

1.3.2 Hydrogel

Hydrogels are three-dimensional, hydrophilic polymer networks that have gained significant attention in controlled drug delivery due to their unique properties, including high water content, biocompatibility, and tunable mechanical strength. These characteristics allow hydrogels to swell in the presence of aqueous environments, enabling them to encapsulate and gradually release therapeutic agents in a controlled manner. The release kinetics can be modulated through alterations in the hydrogel's chemical composition, cross-linking density, and external stimuli, such as pH or temperature changes .Additionally, hydrogels can be designed to respond to biological triggers, like enzyme

activity or specific cellular environments, facilitating targeted delivery to diseased tissues .This specificity is particularly beneficial in applications such as cancer therapy, where localized drug delivery can minimize systemic side effects and enhance therapeutic efficacy. Furthermore, hydrogels can also be integrated with nanoparticles or other carriers to improve drug loading capacity and release profiles, making them versatile platforms for advancing drug delivery technologies .Overall, hydrogels hold great promise in the development of sophisticated drug delivery systems that improve treatment outcomes in various clinical settings [12, 13].

1.3.3 Dendrimer

Dendrimers are highly branched, nanoscale polymers characterized by their unique tree-like structure, which provides a high degree of functionalization and a well-defined architecture. These properties make dendrimers particularly attractive as carriers for controlled drug delivery systems. Their uniform size, low polydispersity, and ability to encapsulate a variety of therapeutic agents, including small molecules, peptides, and nucleic acids, allow for versatile applications in medicine .Moreover, dendrimers can be engineered to exhibit specific surface functionalities, enabling targeted delivery to diseased cells by utilizing ligand-receptor interactions .The multivalency of dendrimers enhances their ability to bind multiple drug molecules, facilitating controlled release profiles that can be modulated based on environmental stimuli such as pH, temperature, or enzymatic activity .Additionally, their capacity to penetrate biological barriers, including cell membranes, further underscores their potential in improving drug bioavailability and

therapeutic efficacy. Overall, dendrimers represent a promising platform for the development of advanced drug delivery systems, enhancing precision and effectiveness in therapeutic applications [14, 15].

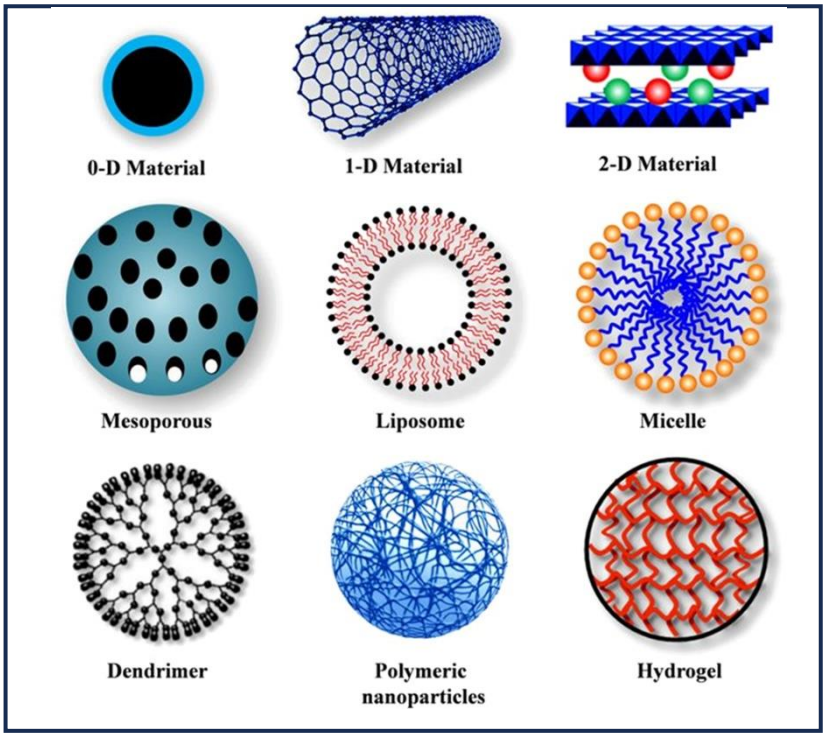

Figure 1.2: Different drug delivery systems for cell specific drug delivery [Singh, A. P., Biswas, A., Shukla, A., & Maiti, P. (2019). Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. Signal transduction and targeted therapy, 4(1), 33.]

1.3.4 Micelles

Micelles are nanoscale aggregates formed from amphiphilic surfactants, consisting of hydrophobic cores surrounded by hydrophilic shells. These unique structures have emerged

as effective carriers for controlled drug delivery, particularly for poorly water-soluble drugs. The hydrophobic core provides an ideal environment for solubilizing hydrophobic therapeutic agents, enhancing their bioavailability [16]. By modifying the composition and architecture of micelles, researchers can achieve precise control over drug loading capacity and release rates. Furthermore, the surface properties of micelles can be tailored to facilitate targeted delivery by attaching specific ligands that recognize and bind to receptors on diseased cells .The stimuli-responsive nature of certain micellar systems allows for controlled release triggered by environmental factors such as pH or temperature changes, making them particularly valuable in applications like cancer therapy .Overall, micelles represent a promising strategy for enhancing the efficacy and safety of drug delivery systems, paving the way for more effective treatments [17].

1.3.5. Polymer

Polymer matrices are increasingly recognized as versatile carriers in controlled drug delivery systems, providing a wide array of advantages such as biocompatibility, biodegradability, and the capacity to sustain the release of therapeutic agents over extended periods. These matrices can be formulated using either natural or synthetic polymers, allowing for flexibility in drug encapsulation techniques, which include physical entrapment and chemical bonding. This approach not only enhances the stability of the drugs but also improves their bioavailability, making it easier for them to reach their intended targets within the body .The design of polymer matrices can be finely tuned by adjusting the polymer composition and cross-linking density, enabling researchers to customize the release profiles of the encapsulated drugs. This tailoring permits the achievement of various release kinetics, such as zero-order or first-order release, depending

on the therapeutic requirements of specific treatments .For instance, in chronic conditions where a steady release of medication is essential, zero-order kinetics may be preferred to maintain consistent drug levels in the bloodstream [18]. Moreover, polymer matrices can be engineered to respond dynamically to specific stimuli, including pH changes, temperature fluctuations, or even the presence of certain biomolecules. This responsive design facilitates targeted drug delivery to particular tissues or cells, enhancing the efficacy of treatments while minimizing side effects .Such targeted strategies are especially beneficial in fields like oncology, where localized delivery can significantly improve therapeutic outcomes by concentrating the drug at the tumor site and reducing systemic exposure. The customization capabilities of polymer matrices make them an attractive option for a wide range of applications, particularly in oncology and the management of chronic diseases. By allowing for controlled and sustained release of therapeutic agents, these systems not only improve patient compliance but also enhance the overall effectiveness of treatment regimens, paving the way for more advanced therapeutic strategies [19].

1.4. Nanoparticles in controlled drug delivery and cancer therapy

Nanoparticles (NPs) utilized in medical diagnostics must possess specific sizes, shapes, and surface characteristics that greatly influence the efficiency of drug delivery and the overall therapeutic effect [20]. For cancer therapy, NPs with diameters ranging from 10 to 100 nm are optimal due to their ability to effectively deliver drugs and leverage the enhanced permeability and retention (EPR) effect. Smaller particles may leak from normal blood vessels or be filtered out by the kidneys [21], whereas larger particles are more susceptible to clearance by phagocytes [22]. Modifying the surface of these nanoparticles, such as by coating them with hydrophilic materials like polyethylene glycol (PEG), can reduce opsonization, thereby improving their circulation time and ability to penetrate tumors [23].

These engineered characteristics are crucial for determining the therapeutic efficacy of NPs in cancer treatment.

1.4.1 Inorganic Nanoparticles

In recent years, inorganic nanocarriers have gained significant attention for both therapeutic and imaging applications due to their numerous advantages, such as a large surface area, high drug-loading capacity, enhanced bioavailability, and reduced toxicity. Commonly used inorganic nanoparticles in cancer treatment include quantum dots, CNTs, LDHs, mesoporous silica, and magnetic nanoparticles, as depicted in Figure 5. Quantum dots, in particular, excel as imaging probes, providing capabilities for long-term, multiplexed imaging and diagnostics [24-26]. These zero-dimensional fluorescent nanoparticles, typically measuring between 1 and 10 nm, are promising for targeted drug delivery and intracellular monitoring but face challenges such as hydrophobicity and aggregation. Enhancing their water solubility and bioactivity can be achieved by coating quantum dots with polar species or ligands. Multifunctional quantum dots that incorporate imaging agents, hydrophobic drugs, and targeting molecules are being explored for effective cancer targeting and therapy. Recently, polymer-coated quantum dots have shown potential as vehicles for cancer diagnostics and image-guided chemotherapy [27]. Gold nanoparticles (AuNPs), especially mixed monolayer-protected clusters with a gold core, have been extensively studied for their drug delivery capabilities. Their non-toxic gold core, combined with surface modifications, facilitates drug accumulation in tumors and addresses drug resistance challenges. AuNPs are also being investigated for multimodal cancer treatments, including gene therapy, photothermal therapy, and immunotherapy [28].

CNTs, which are one-dimensional nanomaterials formed from rolled sheets of graphene, have applications in near-infrared photothermal ablation therapy, raising tumor temperatures upon light exposure. Functionalized, water-soluble CNTs are being explored for efficient gene and drug delivery, effectively crossing biological barriers without causing toxicity. Chemotherapeutic agents can be linked to CNTs through surface functional groups or polymer coatings. In the context of immunotherapy, CNTs act as carriers for antigens, enhancing the immunogenicity of tumor-derived peptides to stimulate a robust immune response [29,30].

Mesoporous silica nanoparticles (MSNs) excel in drug delivery due to their extensive internal pore volume, which maximizes drug encapsulation. Their supramolecular components can function as caps, regulating drug capture and release. MSNs offer enhanced pharmacokinetics, treatment efficacy, and stability, positioning them as prime candidates for drug delivery applications. Moreover, porous silicon nanoparticles demonstrate potential in immunotherapy by promoting antigen cross-presentation and enhancing immune responses [31].

Magnetic nanoparticles (MNPs), typically composed of metal or metal oxide materials, are often coated with organic substances to improve their stability and biocompatibility. They show promise in cancer treatments involving chemotherapy and gene therapy and can facilitate magnetic hyperthermia, which enables tumor thermal ablation as an alternative therapeutic strategy [32].

LDHs, a type of inorganic nanocarrier, are attracting attention for their biocompatibility, anion exchange properties, high drug-loading capabilities, and pH-responsive release mechanisms. Composed of divalent and trivalent metal ions, LDHs can encapsulate drugs

between their layers, protecting them while allowing for targeted delivery and functionalization [33].

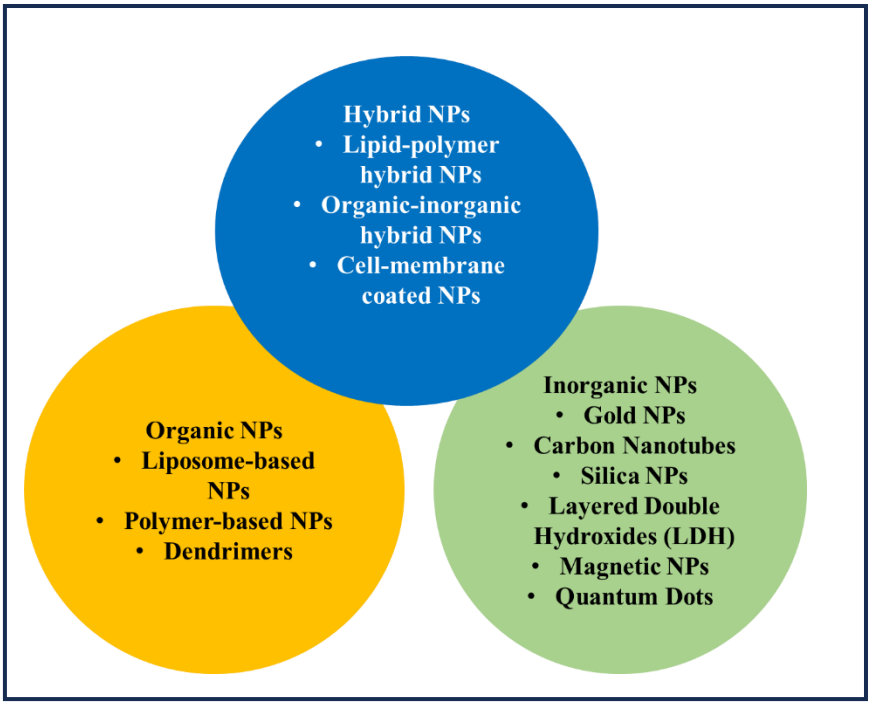

Figure 1.3: Nanoparticles (NPs) for cancer therapy encompass various types including organic, inorganic, and hybrid NPs.

1.4.2. Organic Nanomaterials

Polymer-based nanoparticles are typically solid, biocompatible, colloidal systems that are biodegradable and possess nanoscale dimensions. These materials can be easily modified to achieve desired properties such as drug loading efficiency and biodistribution. They can be synthesized from synthetic polymers (e.g., PLA, PLGA, PCL) [34-36] or natural polymers (e.g., gelatin, chitosan, cyclodextrin) [37-42], allowing for controlled drug

delivery through various mechanisms. Synthetic polymers generally provide sustained release benefits compared to their natural counterparts. FDA-approved examples, such as PLA and PLGA, are widely investigated for drug delivery applications. Techniques like drug conjugation and precise parameter manipulation enable fine-tuning of drug release profiles, enhancing cancer treatment effectiveness [28].Liposomes, which have been studied for decades, consist of a lipid bilayer surrounding a drug-containing core, mimicking biological membranes to improve therapeutic delivery. Evolving through multiple generations, liposomes are crucial in cancer therapy for delivering agents like doxorubicin and paclitaxel [43], reducing cardiotoxicity, and facilitating drug combination strategies to overcome resistance.

1.4.3 Hybrid Nanoparticles

The combination of organic and inorganic nanoparticles can enhance drug delivery efficacy while reducing resistance. Lipid-polymer hybrid nanoparticles have shown promise for treating a variety of cancers by effectively encapsulating both hydrophilic and hydrophobic drugs. Liposome-silica hybrids (LSHs) are particularly effective in delivering drugs that can induce cancer cell death. Advanced nano-in-micro platforms improve drug delivery and enhance cell death in drug-resistant cancers. Hybrid systems, including combinations of CNTs and chitosan, can increase anticancer activity while minimizing toxicity. Metal multilayer half-shells and PLGA hybrids are designed for targeted drug delivery and thermal therapy to destroy tumor cells. Innovative approaches, such as cell membrane coating technologies, enhance the biological characteristics of nanoparticles, with coatings derived from leukocytes, red blood cells, platelets, cancer cells, and bacteria showing promise. For example, the use of leukocyte-derived coatings on nanoporous silicon particles can reduce phagocyte clearance, extending circulation time and improving tumor accumulation. Similarly, cancer cell membrane-coated mesoporous silica nanoparticles

enhance stability and targeting, while dual-membrane coatings can increase longevity in circulation. Multistage nanoparticle delivery systems, such as those utilizing protease-sensitive designs, can facilitate deeper penetration into tumors [44].

1.4.4 Targeting Mechanisms

Effective targeting of cancer cells is essential for the success of nanoparticle-based drug delivery systems, as it increases efficacy while protecting normal cells. Extensive research has been dedicated to designing NP-based drug targeting systems, emphasizing the importance of understanding tumor biology and the interactions between nano-carriers and tumor cells. Targeting mechanisms can be categorized into passive and active strategies.

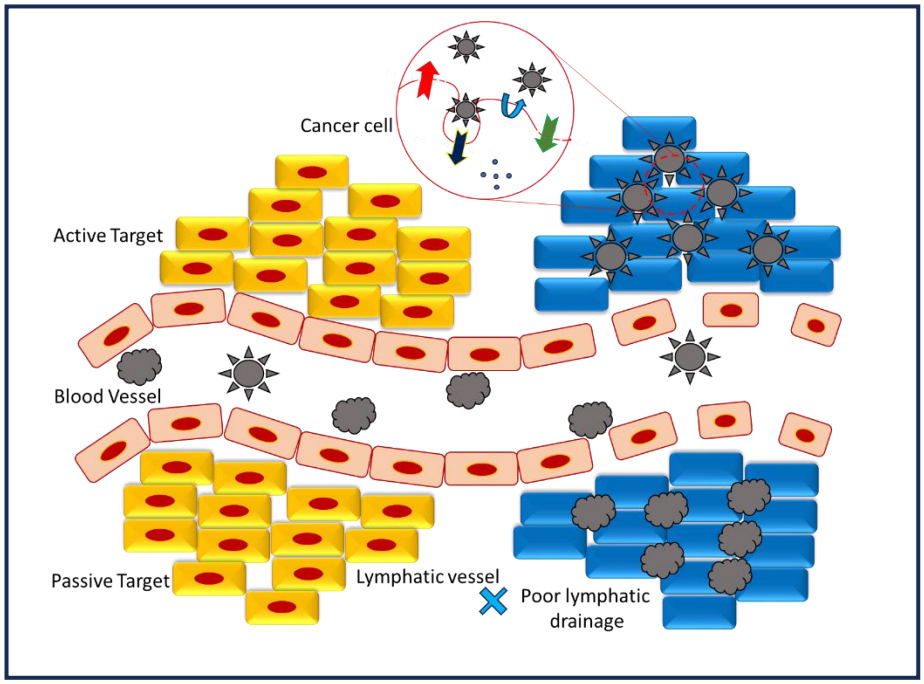

Figure 1.4: Passive and active targeting of nanoparticles (NPs) to cancer cells enhances therapy efficacy while minimizing systemic toxicity. Passive targeting utilizes the enhanced permeability and retention (EPR) effect, leveraging increased vascular permeability and weakened lymphatic drainage. Active targeting involves ligand-receptor interactions, with receptors on cancer cells including transferrin, folate, glycoproteins, and EGFR[Yao, Y.,

Zhou, Y., Liu, L., Xu, Y., Chen, Q., Wang, Y., ... & Shao, A. (2020). Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. *Frontiers in molecular biosciences*, *7*, 193.]

Passive targeting leverages the EPR effect, which exploits the unique characteristics of tumor vasculature, including increased permeability and impaired lymphatic drainage, allowing nanoparticles to accumulate in tumors. In contrast, active targeting involves the use of ligands on nanoparticles to bind to overexpressed receptors on cancer cells, facilitating receptor-mediated endocytosis and enabling more precise drug delivery, particularly for macromolecular drugs such as proteins and siRNA. Ligands used for active targeting include monoclonal antibodies, peptides, and vitamins that interact with receptors such as the transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR). While passive targeting exploits the inherent characteristics of tumors for drug delivery, active targeting allows for more selective interactions, improving therapeutic outcomes.

1.4.5 Targeting Endothelial Cells

Some nanoparticles are designed to target the endothelial cells involved in angiogenesis rather than the cancer cells directly. Interactions between vascular endothelial growth factor (VEGF) and its receptors (VEGFR-2 and VEGFR-3) are pivotal in vascularization processes [45]. Liposomes that simultaneously target these receptors can enhance treatment efficacy [46]. Integrin's, particularly avb3, play a critical role in tumor cell migration, and cationic nanoparticles that incorporate αvβ3 ligands show promise for gene delivery. The αvβ3 integrin's link to VEGFR-2 signalling may also improve the effectiveness of anti-

VEGFR therapies. Furthermore, vascular cell adhesion molecule 1 (VCAM-1) is expressed on tumor endothelium, aiding in the efficient delivery of NP-based drugs. VCAM-1-targeted nanoparticles have demonstrated significant efficacy in preclinical breast cancer models. Matrix metalloproteinase (MMPs) in the tumor microenvironment contributes to remodelling of the extracellular matrix, facilitating neovascularization [47].

1.4.6. Overcoming Drug Resistance Mechanisms

Drug resistance remains a significant challenge in cancer treatment, undermining the efficacy of various therapeutic approaches and contributing to poor prognoses. Mechanisms underlying drug resistance include overexpression of ATP-binding cassette (ABC) transporters, dysfunctional apoptotic pathways, and hostile tumor microenvironments.

1.4.7. Targeting the Hypoxic Tumor Microenvironment

Hypoxia in tumors often induces a drug-resistant state, increasing tumor heterogeneity. Nanoparticles designed to target hypoxia-inducible factor 1α (HIF-1α), as well as NPs containing HIF-1α siRNA and heat shock protein 90 (HSP90) inhibitors, show promise in countering drug resistance [48]. A novel approach utilizing a liposomal nanodrug that incorporates glucose oxidase.

1.5. LDH Nanoparticles in controlled drug delivery and cancer therapy

LDH nanoparticles have emerged as a promising platform for controlled drug delivery, particularly in the treatment of melanoma, one of the most aggressive forms of skin cancer. These nanocarriers offer unique properties that facilitate targeted drug delivery, enhance therapeutic efficacy, and minimize systemic toxicity. This discussion explores the

advantages of LDH nanoparticles in melanoma treatment, their mechanisms of action, and the potential for future applications in cancer therapy.

1.5.1. Structure and Composition of LDH Nanoparticles

LDHs, also known as anionic clays, are composed of positively charged metal hydroxide layers interspersed with charge-balancing anions. Commonly used metal cations include magnesium, aluminium, and zinc, while interlayer anions can be varied, including carbonate, phosphate, or even drug molecules. This layered structure allows for high drug-loading capacities and the possibility of sustained release, making LDH nanoparticles particularly suitable for drug delivery applications in oncology.

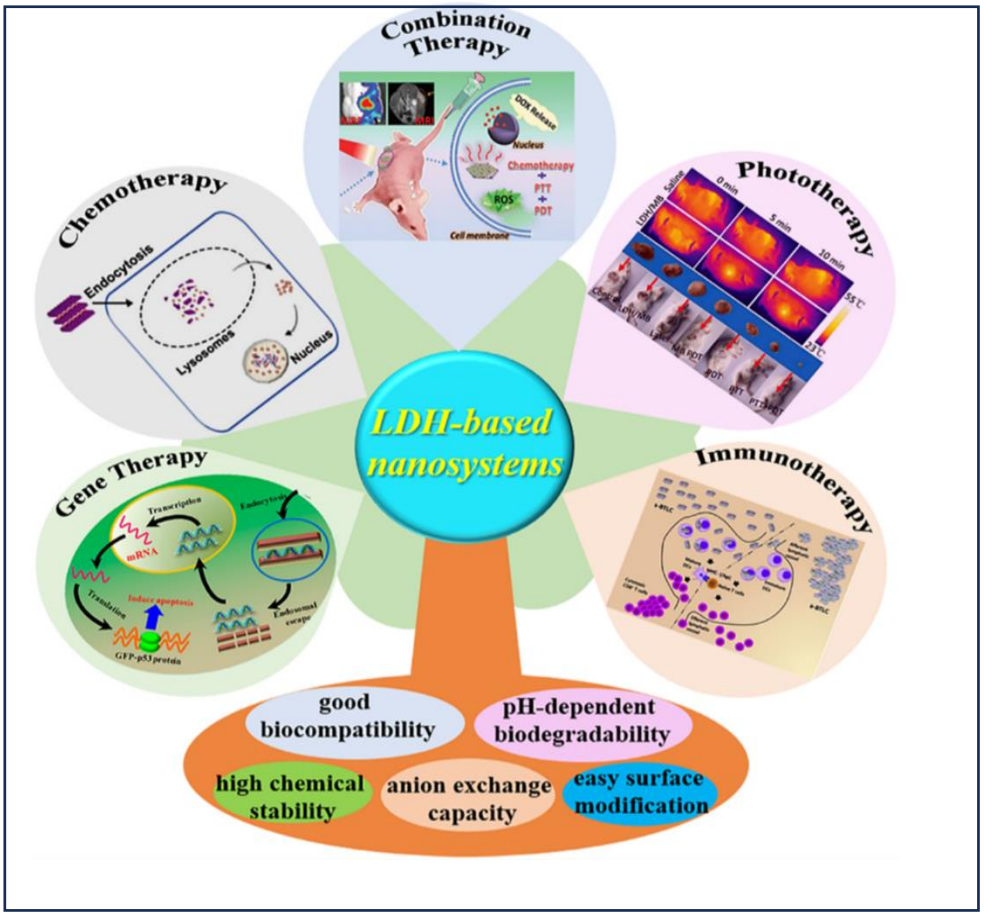

Figure 1.5. Advantages and different biomedical applications of LDH (Materials & Design, 109298)

The tunable nature of LDHs allows researchers to modify their physical and chemical properties. By varying the metal cation composition and the nature of the interlayer anions, it is possible to tailor LDH nanoparticles for specific therapeutic agents and to optimize their release profiles. This customization is crucial for addressing the unique challenges associated with melanoma treatment, including drug resistance and the need for targeted delivery to tumor sites.

1.5.2. Mechanisms of Drug Delivery

One of the key advantages of LDH nanoparticles in drug delivery is their ability to achieve controlled release. The interlayer anions can be designed to respond to various stimuli, such as changes in pH or temperature. This is particularly relevant for melanoma treatment, as the tumor microenvironment is often characterized by acidic conditions due to increased metabolic activity. When LDH nanoparticles are introduced into the acidic environment of the tumor, the release of the encapsulated drug can be accelerated, providing a localized therapeutic effect.

Furthermore, LDHs can facilitate the co-delivery of multiple therapeutic agents. This is particularly beneficial in melanoma treatment, where combination therapy is often necessary to overcome drug resistance. For instance, LDH nanoparticles can be engineered to deliver chemotherapeutics alongside RNA-based therapies, such as siRNA or mRNA,

that targets specific oncogenes or pathways involved in melanoma progression. This multi-modal approach not only enhances the therapeutic efficacy but also helps to mitigate potential side effects associated with high doses of a single agent.

1.5.3. Targeted Delivery and Biocompatibility

Targeted drug delivery is crucial in minimizing the off-target effects that are common with conventional chemotherapy. LDH nanoparticles can be functionalized with targeting ligands, such as antibodies, peptides, or small molecules that specifically bind to overexpressed receptors on melanoma cells. This targeted approach enhances the accumulation of therapeutic agents at the tumor site, reducing systemic toxicity and improving treatment outcomes.

Moreover, LDH nanoparticles exhibit excellent biocompatibility due to their inorganic nature and the ability to degrade in physiological conditions. Studies have shown that LDHs do not elicit significant immune responses, making them suitable candidates for long-term therapeutic applications. Their biodegradability ensures that they do not accumulate in the body.

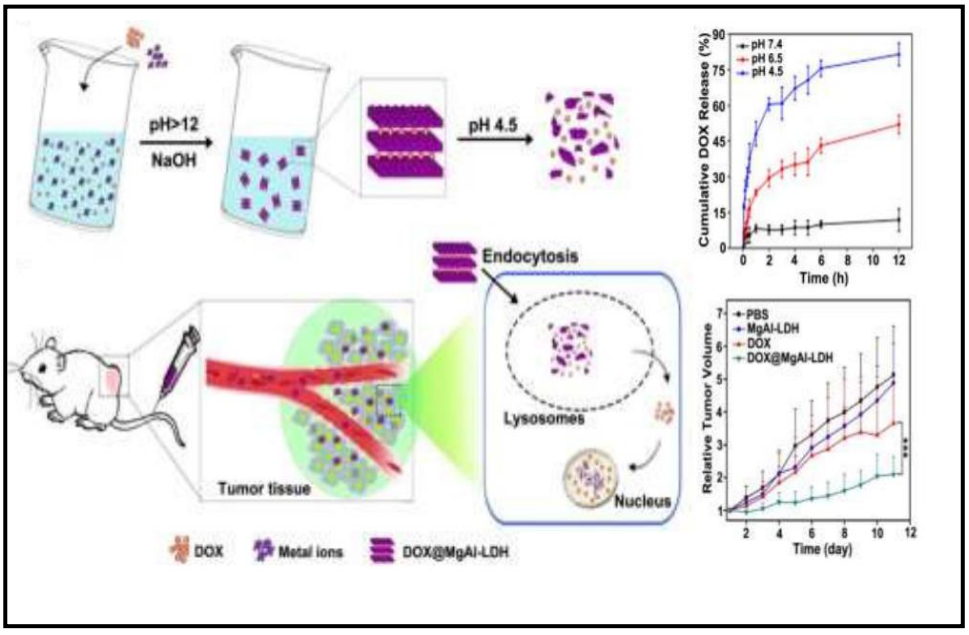

Figure 1.6. Cancer Treatment by using Dox intercalated Mg-Al based LDH (Journal of Materials Chemistry B, 2018, *6*(36), 5768-5774)

1.5.4. Overcoming Drug Resistance

Melanoma cells often develop resistance to conventional therapies through various mechanisms, including the upregulation of efflux pumps, alteration of drug targets, and changes in cellular signalling pathways. LDH nanoparticles can be strategically designed to overcome these resistance mechanisms. For example, they can be loaded with drugs that inhibit the function of efflux pumps or modulate the signalling pathways that contribute to drug resistance.

Additionally, the ability to deliver RNA-based therapies alongside conventional chemotherapeutics can target the underlying genetic factors contributing to resistance. By silencing specific genes involved in drug resistance, LDH nanoparticles can enhance the sensitivity of melanoma cells to existing treatments.

1.5.5. Future Perspectives

LDH nanoparticles represent a versatile and effective platform for controlled drug delivery in melanoma treatment. Their tunable properties, ability to achieve controlled release, and potential for targeted delivery make them an attractive option for addressing the challenges associated with melanoma therapy. As research in this field progresses, the integration of LDH nanoparticles into clinical practice may offer new avenues for improving the efficacy and safety of melanoma treatments.

Future studies should focus on the large-scale production and clinical translation of LDH nanoparticles. Investigating the pharmacokinetics and long-term safety profiles *in vivo* will be essential for their successful application in cancer therapy. Additionally, exploring the potential of combining LDH nanoparticles with immunotherapeutic approaches could further enhance their therapeutic impact against melanoma. Overall, LDH nanoparticles hold significant promise for revolutionizing drug delivery in oncology and improving patient outcomes in melanoma treatment [49-56].

1.6. Grafted Polymers for Controlled Drug Delivery: Focus on Polyurethane Grafted Polymers

Grafted polymers represent a significant advancement in the field of controlled drug delivery systems, combining the benefits of both polymer science and biochemistry to enhance therapeutic efficacy. These materials consist of a backbone polymer to which side chains or "grafts" of different polymers are covalently attached. This grafting modifies the physical and chemical properties of the base polymer, enabling tailored characteristics for specific applications, particularly in drug delivery.

1.6.1 Mechanism of Action

The unique architecture of grafted polymers allows for controlled release mechanisms through various strategies. The side chains can influence the hydrophilicity and

hydrophobicity of the overall polymer, affecting drug solubility and release profiles. For instance, when used as drug carriers, grafted polymers can respond to environmental stimuli such as pH, temperature, or the presence of specific enzymes, allowing for on-demand drug release at targeted sites.

1.6.2Polyurethane Grafted Polymers

Among grafted polymers, polyurethane (PU) grafted polymers have garnered attention due to their excellent biocompatibility, mechanical properties, and versatility. Polyurethanes can be synthesized with varying degrees of hydrophilicity by altering the composition of the soft and hard segments within the polymer. This flexibility makes PU grafted polymers suitable for a range of biomedical applications, including drug delivery.

PU grafted polymers can encapsulate hydrophobic drugs effectively, providing a controlled release profile that can be fine-tuned based on the specific needs of the treatment. Their tunable mechanical properties also make them suitable for various applications, from soft tissue engineering to targeted drug delivery systems. Furthermore, the incorporation of bioactive molecules into the PU matrix can enhance the therapeutic outcomes by promoting cellular interactions.

1.6.3. Advantages and Future Directions

The primary advantages of polyurethane grafted polymers in drug delivery include their biodegradability, ease of modification, and ability to form stable drug-polymer complexes. These characteristics not only enhance drug solubility but also allow for a sustained release over extended periods, minimizing the need for frequent dosing and improving patient compliance.

Looking ahead, research into PU grafted polymers will likely focus on optimizing their formulations for specific therapeutic applications, exploring their interactions with biological systems, and evaluating their long-term safety profiles. The development of multifunctional grafted polymers that can deliver multiple therapeutic agents simultaneously could also represent a promising avenue for future investigations [57-60].

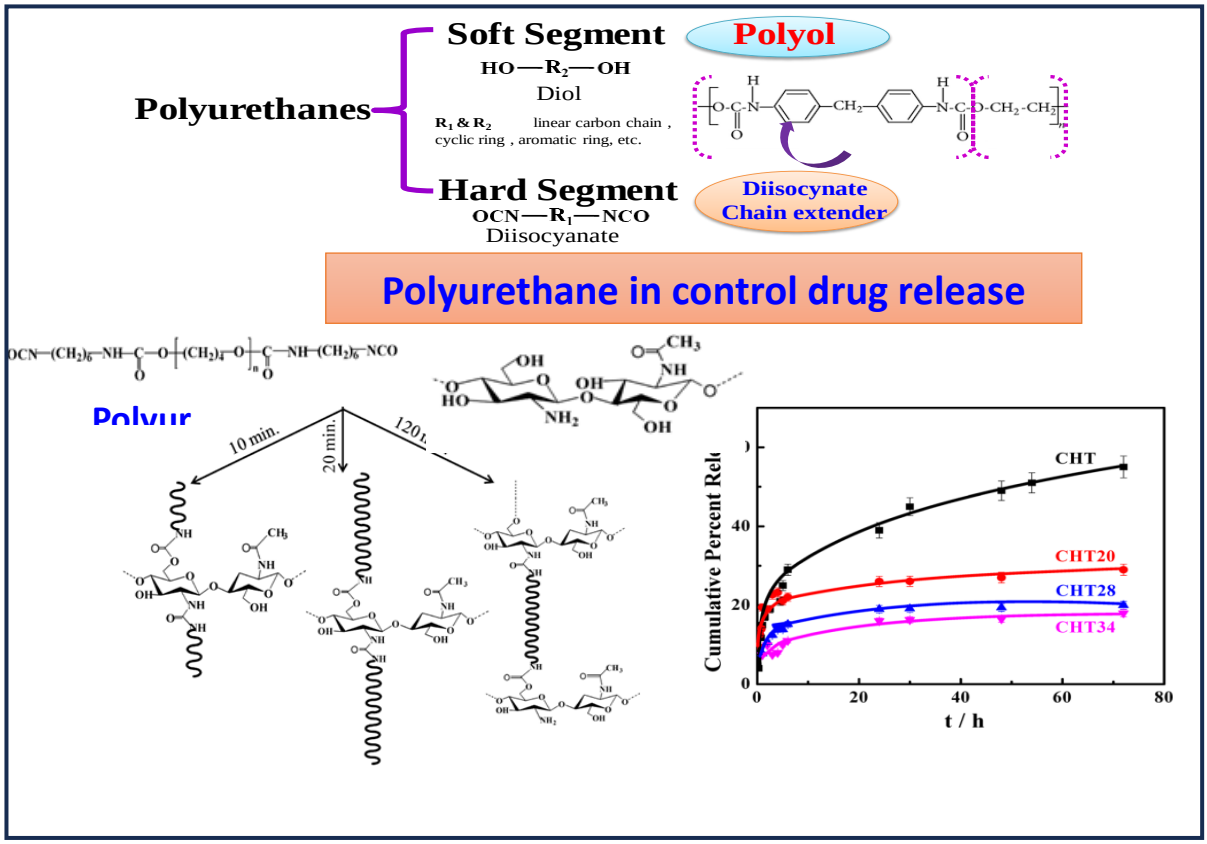

Figure 1.7. Polyurethane grafted materials for controlled drug delivery **(Macromolecules, 48(8), 2654-2666)**

1.7. Objective of the present thesis

(i) Enhancing Targeting Efficiency

We aim to significantly improve targeting efficiency at both the tissue and cellular levels, ensuring precise delivery of therapeutic molecules. By overcoming biological barriers such as the blood-brain barrier, intestinal lining, skin, lung tissues, and vaginal mucosa, we can enhance the bioavailability and efficacy of drugs. This approach not only can maximize therapeutic effects but also can minimize systemic side effects, leading to safer and more effective treatments tailored to specific conditions.

(ii) Developing Next-Generation Long-Acting Delivery Technologies

Our focus is on pioneering long-acting drug delivery systems that optimize pharmacokinetics (PK) and enable pre-programmed pulsatile release of therapeutics over extended periods. These advanced technologies will allow for sustained therapeutic levels in the bloodstream, reducing the need for frequent dosing and improving patient adherence. By controlling release profiles, we can better match the pharmacodynamics of drugs with patient needs, leading to improved outcomes.

(iii)Personalized Drug Delivery Technologies

We are committed in advancing drug delivery technologies that will facilitate personalized therapies. By leveraging individual patient data, including genetic profiles, disease states, and metabolic responses, we can design and implement tailored delivery systems that will maximize therapeutic benefits while minimizing adverse effects. This patient-centric approach ensures that treatments are not only effective but also aligned with the unique physiological characteristics of each individual.

(iv) Merging Advanced Technologies with Drug Delivery

Integrating cutting-edge technologies such as machine learning (ML) and artificial intelligence (AI) into drug delivery systems holds the potential to revolutionize therapeutic strategies. By utilizing predictive analytics and real-time data processing, we can optimize drug formulation, personalize delivery mechanisms, and anticipate patient responses. This convergence of AI with drug delivery technologies will enable smarter, more adaptive systems that enhance treatment efficacy and pave the way for innovative therapeutic solutions.

1.8 Content and scope of the present work

LDHs offer numerous advantages for drug delivery, including enhanced stability, biocompatibility, and the ability to encapsulate a wide variety of drugs. This versatility allows for tailored release profiles optimized for specific therapeutic needs, ensuring that drugs are delivered effectively while minimizing side effects. The non-toxic nature of LDHs, combined with their compatibility with biological systems, makes them as promising candidates for pharmaceutical applications. By optimizing the design of LDHs, researchers can develop systems that can respond to specific physiological conditions, facilitating sustained drug release. Their stable physicochemical properties, high surface area, and anion exchange capacity make them efficient inorganic nanocarriers.

Functionalized LDH materials can serve as grafted receptors for drugs, enhancing controlled delivery across cellular membranes. This innovative approach aims to improve patient adherence and reduce the overall costs of treatments.

In one of our studies, we developed tumor-targeted drug delivery systems utilizing lithium-aluminium (Li-Al) LDH through a co-precipitation method. These biodegradable nanocarriers effectively facilitate synergistic interactions with doxorubicin (DOX), achieving an optimal balance between circulation lifetimes, drug loading capacity, and tumor-specific uptake. Theoretical investigations using density functional theory (DFT) highlighted the bonding interactions and electronic structure of LDHs with DOX, demonstrating their potential as effective drug carriers. *In vitro* and *in vivo* assessments, particularly with melanoma-bearing mice, revealed improved biocompatibility and significant synergistic anticancer activity of these nanoformulations. Notably, Li-Al-based LDH carriers significantly reduce the toxic effects typically associated with conventional chemotherapy through the use of an injectable hydrogel that enables controlled drug release directly at the tumor site. This ability to regulate drug delivery enhances therapeutic efficacy while minimizing toxicity, paving the way for multifunctional nanomedicine strategies in cancer treatment.

In a subsequent study, we synthesized functionalized LDHs to improve cell-killing efficacy. Previously, our formulations not only targeted cancer cells but also affected 40% of normal healthy cells, indicating a lack of selectivity. To address this, we synthesized polyurethane via a reaction between poly (tetramethylene glycol) (PTMG) and hexamethylene diisocyanate (HMDI), creating a polyurethane-grafted Li-Al LDH nanocomposite. This new formulation demonstrated sustained release of DOX, outperforming pure polyurethane in drug delivery. *In vitro* studies using cancer and normal cell lines showed that the cancer cell killing efficacy reached 95%, while the normal cell killing was reduced to 30%.

Furthermore, extensive analysis of the mechanical properties revealed that the elongation at break for the nanocomposite was significantly higher compared to pure polyurethane, indicating excellent flexibility and stretchability—crucial attributes for biomedical applications.

We also conducted *in vivo* studies using a melanoma model with luciferase-expressing B16-F10 cells. Bioluminescence imaging and qualitative analysis of tumor volume growth confirmed the formulation's efficacy in effectively killing melanoma cells. Supporting evidence from Western blotting, RT-PCR, and cell cycle analysis reinforced the effectiveness of the polyurethane-grafted LDH nanocomposite as a targeted drug delivery system. Overall, our research suggests that this innovative nanoformulation offers a promising approach for cell-specific drug delivery in cancer therapy.

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