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RESEARCH ARTICLE
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NOVEL DRUG DELIVERY OF NANOPARTICLE-BASED CONTROLLED RELEASE SYSTEM AND THEIR EFFECTS ON TARGETTING CANCER CELLS-REVIEW

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ABSTRACT:

Background: Nanoparticle-based drug delivery systems (NDDS) have gained significant attention for their potential to improve cancer therapy outcomes. These systems offer the ability to enhance drug delivery efficacy, improve therapeutic outcomes, and reduce adverse effects, making them a promising approach in cancer treatment.

Objective: This systematic review aims to explore advancements in NDDS from 2007 to 2022, focusing on their role in revolutionizing cancer therapy by enhancing drug delivery efficacy, improving therapeutic outcomes, and minimizing side effects.

Methodology: A comprehensive survey was conducted, analyzing sixty-five articles from reputable sources, including Google Scholar, Critical Reviews in Biotechnology, and various nanomedicine-focused publications. The review covers various types of nanoparticles, such as liposomes, polymer micelles, dendrimers, and inorganic nanoparticles, and their applications in cancer therapy.

Result: The review highlights the potential of different nanoparticles in improving cancer therapy. It discusses the use of magnetic and gold nanoparticles in hyperthermia, targeted drug delivery, and gene therapy. The study also emphasizes the importance of understanding nanoparticle properties and their interactions with biological systems to optimize therapeutic outcomes. **Conclusion:** While significant advancements in NDDS have been made, challenges remain in optimizing nanoparticle design, refining targeting strategies, and facilitating clinical translation. Continued research is essential to fully realize the potential of NDDS in cancer therapy.

Keywords: Nanoparticle-based drug delivery systems (NDDS), Cancer therapy, Drug delivery efficacy, Therapeutic outcomes, Liposomes, Targeted drug delivery, Clinical translation.

INTRODUCTION

The CNP-based nanoparticles in drug delivery have been utilized in various diseases treatment, including cancer-related diseases, gastrointestinal diseases, pulmonary diseases, ocular infections, and drug delivery across the blood-brain barrier. CNP possessed several features that enabled its utilization as a vital drug delivery vector, such as enhance delivery and therapeutic efficacy of drugs, improved intracellular accumulation and controlled release properties. Similar to other nanoparticulate delivery systems, CNP has a protective layer after the encapsulation of therapeutics into the core of nano-

particles. The conventional methods of drug consumption such as oral delivery, sublingual delivery, and rectal delivery are always preferred by patients due to the ease of consumption widespread acceptance by patients. However, the therapeutic efficacy of these medications is often less desired as the drugs that are consumed, especially orally, need to go through many different paths such as the digestive tract, gastrointestinal tract, and liver to reach the target site, which may lead to the cleavage or degradation by the enzymes or extreme pH environment before they reach the site of absorption and bloodstream (1). The research of nanotechnology and its many applications in a variety of scientific fields is ever expanding. Medical applications of nanotechnology have the potential to revolutionize both the diagnosis and treatment of diseases. Examples of future applications include the use of nanotechnology to assist in drug delivery, in vitro and in vivo diagnostics, and the production of improved biocompatible materials.

Advantages of Nanoparticle

Nanoparticle drug delivery systems are typically below 1000-nm size range.

Nanoparticle drug delivery systems offer the following advantages:*The ability to travel through small capillaries and avoid clearance by phagocytes*The ability to penetrate cells and tissue gaps to arrive at target organs.*The ability to display controlled release properties which are a function of the particle's biodegradability, pH, ion or temperature sensitivity.*Improve the utility of various drugs and reduce side effects (2).*Nanoparticles are promising tools for the efficient delivery of these drugs to the gastrointestinal tract (3)

The nanotechnological approach, first framed in the 1950's by Richard P. Feynman, was the constitutive force to establish nanomedicine as a paramount section in science and medical treatments. From the beginning nanomedicine developed rapidly, driven by tremendous progress in techniques (4). In 1959, Feynman was the first physicist to introducethe notion of nanotechnology in the lecture entitled "There's Plenty of Room at the Bottom". This concept initiated remarkable developments in the arena of nanotechnology (5) Nanotechnology is the study of extremely tiny things and is basically the hub of all science disciplines including physics, chemistry, biology, engineering, information technology, electronics, and material science. The structures measured with nanotechnology range from 1–100 nm at the nanoscale level. Nanoparticles have different material characteristics because of submicroscopic size and also provide practical implementations in a wide range of fields including engineering, drug de livery, nanomedicine, environmental indemnification, and catalysis, as well as target diseases such as melanoma and cardiovascular diseases (CVD), skin diseases, liver diseases, and many others (6)

Roles of Nano Particles in Drug Delivery System

Over Recent years advancement in nanoparticles drug delivery is widely expected to change the landscape of pharmaceutical industries for the foreseeable future. Nanotechnologies have become a significant priority worldwide At nanosize range, the properties of materials differ substantially from bulk materials of the same composition, mostly due to the increased specific surface area and reactivity, which may lead to increased bioavailability and toxicity. Thus, for the assessment of sustainability of nanotechnologies, methods of manufacturing Nanoparticles, properties have to be studied (6). Using nanoparticles, it may be possible to achieve improved delivery of poorly water soluble drugs by delivering drug in small particle size increase the total surface area of the drugs allowing faster dissolution in blood stream. Faster the dissolution translates in to faster absorption by human body targeted delivery of drugs in a cellular tissue-specific manner (6).

METHODOLOGY

To write a systematic review on novel drug delivery of control release dosage form, effects on cancer, and available targeting modes; a literature survey has been conducted from 2007 to 2022. Key-words and truncation techniques were used for the collection of relevant literature from Google Scholar, Critical Reviews in Biotechnology, Journal of Nanomedicine & Nanotechnology, International

Journal of Research in Pharmaceutical and Biomedical Sciences, International Journal of Nanotechnology and Nanomedicine.Sixty-five articles on novel drug deliver of control releases dosage form and effects on cancer were downloaded; forty-one chosen after abstracting relevant information from the studies and assessing quality, data synthesized and presented by following (Figure. 1). The diagram details how studies were identified, the results of abstract screening, the results of full text eligibility assessment; a breakdown of reasons for exclusion, and details of included studies. Full-text eligible articles were forty-six. All the articles were evaluated for their quality; type of journal, data collection methods, significance values. (See Table 1).

Release Kinetics for Control Release Dosage Forms

Nanoparticles face unique challenges in controlling drug release kinetics, due to the large surface area per volume ratio and the short diffusion distance. To develop nanoparticles with desirable release kinetics for target applications, it is important to understand the mechanisms by which a carrier retains and releases a drug, the effects of composition and morphology of the carrier on the drug release kinetics, and current techniques for preparation and modification of nanoparticles (7) One of the main goals of release kinetics control is to maintain the drug level in blood within the therapeutic window, between the minimum effective concentration (MEC) and the minimum toxic concentration (MTC) (Siegel, 2012). When a drug is administered as a single large dose, the drug level is elevated above MTC, causing toxic side effects, and then rapidly drops below the MEC. Multiple dosing with a certain interval may reduce the fluctuation of drug levels in plasma but can face (8) The effects of nanoparticle (NP) properties, such as size, shape and surface charge, on their efficacy and toxicity have been studied extensively (9) The kinetic models were those which have been Used in interpretation of drug release data Kinetic study of drug release is often useful in Obtaining one or two physically meaningful Parameters which are employed for comparative Purposes and relating the release parameter with Important parameters such as bioavailability. Further more a kinetic parameter can be used to Study the influence of formulation factors on the Drug release for optimization as well as control of Release. (See Table 2). (10)

❖ Zero Order

Drug dissolution from dosage forms that do not Disaggregate and release the drug slowly can be represented by the equation (11) Q0 - Qt = K 0t Rearrangement of equation (3) yields: Q t = Q 0 + K 0t Where Qt is the amount of drug dissolved in time t,Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K 0 is the zero order release constant expressed in units of concentration/time (12). To study the release kinetics, data obtained From in vitro drug release studies were plotted accumulative amount of drug released versus time.

❖ First Order

This model has also been used to describe absorption and/or elimination of some drugs Although it is difficult to conceptualize this mechanism. On a theoretical basis. The release of the drug. Which followed first order kinetics can be expressed. By the equation: dC/dt= -Kc Where K is first order rate constant expressed in units of time-1. Equation (5) can be expressed as: Log C = log C0 -Kt / 2.303 (16) Where C0 is the initial concentration of drug, k is the First order rate constant, and t is the time (13). The Data obtained are plotted as log cumulative percentage of drug remaining vs. Time which would yield a straight line with a slope of -k/2.303 (14).

In Nanoparticle-Based Drug Delivery Systems, several parameters can influence the Release Kinetics of the encapsulated drug.

Nanoparticle size influences drug release, with smaller particles offering faster release due to a larger surface area-to- volume ratio. Surface modifications using ligands, polymers, or coatings can control interactions with the biological environment, affecting release rates.*Polymer composition, such as PLGA or PEG, and molecular weight influence degradation and diffusion, while the strength of drug-

polymer interactions typically determines release speed, with stronger interactions slowing release.*Drug loading levels impact the release profile, often causing an initial burst followed by controlled release. The encapsulation method (e.g., emulsification, solvent evaporation) and nanoparticle degradation rate, which depend on polymer composition and environmental conditions, are crucial for release kinetics. pH- and thermoresponsive nanoparticles can tailor release based on environmental changes. Hydrophilicity/hydrophobicity balance affects drug solubility and diffusion, and crosslinking density in polymers influences diffusion rates. Lastly, drug crystallinity, with amorphous drugs generally dissolving faster than crystalline ones, also affects release (14). *The relationship between drug release kinetics and therapeutic efficacy has been extensively studied. For instance, the release kinetics of nanoparticles, such as those containing docetaxel and wortmannin, significantly impact their efficacy both in vitro and in vivo. While nanomedicines hold great promise for clinical applications, only a few have been approved and are currently available on the market. Researchers are actively exploring strategies to enhance control over drug release, particularly for cancer treatment, to improve therapeutic outcomes (15).

In-Vitro release of Nanoparticle Polymer

The in vitro release study is essential for evaluating the safety, efficacy, and quality of nanoparticle-based drug delivery systems, yet there is no standardized regulatory method. This variability in testing complicates direct comparisons between different systems. Herein, we propose a novel sample and separate (SS) method that combines the United States Pharmacopeia (USP) apparatus II (paddle) with a well-validated centrifugal ultrafiltration (CU) technique, effectively separating free drugs from nanoparticles. Polymeric drug nanoparticles were prepared using a four-stream multi-inlet vortex mixer with d-α-tocopheryl polyethylene glycol 1000 succinate as a stabilizer. Itraconazole, cholecalciferol, and flurbiprofen were selected to create nanoparticles under 100 nm in size. Compared to the dialysis membrane (DM) method and SS methods using syringe filters, this novel SS
+ CU technique demonstrated superior accuracy and repeatability in providing in vitro release kinetics of nanoparticles. Interestingly, the DM method appeared to inaccurately estimate nanoparticle release kinetics. This work introduces an advanced analytical technique for studying in vitro drug release from polymeric nanoparticles, potentially enhancing the development of in vitro- in vivo correlations for these systems (Figure 2). (16)

Physiological effects on Tumor Microenvironment (TME)

Possesses a variety of unique properties and plays a critical role in the occurrence, invasion and metastasis of tumors. However, the characteristic difference between tumor tissues and normal tissues is also the theoretical basis for designing intelligent responsive NDDS (20). srNPs can respond to various endogenous stimuli in the TME, and their properties, such as shape, size, surface charge and hydrophilicity, could be changed after reaching the tumor areas (21). These changes can promote the accumulation, penetration, cellular uptake or drug release of nanoparticles, and ultimately enhance the anti-tumor therapeutic effect (22).

PH-Responsive Nanocarriers

Due to the Warburg effect, the acidic microenvironment of solid tumors can be used to achieve tumor-specific delivery of srNPs (20). The pKa values of these structures are close to the pH of the intercellular matrix, so their functional groups can be protonated in the TME with a lower pH, resulting in the destruction of the hydrophilic– hydrophobic balance of nanoparticles, thus causing structural changes, including rearrangement, expansion or disintegration (22). Typical acid- sensitive groups include histidine, tertiary amine and sulfonamide structures. The second strategy is based on acidlabile chemical bonds, which can stably exist under neutral conditions and break under acidic conditions (23). use pH (low) insertion peptides (pHLIP), which could weakly interact with the cell membrane under neutral conditions and insert into the cell membrane and form stable transmembrane

complexes in an acidic environment, thus promoting the cellular uptake of nanoparticles (24)

Hydrophobic-to-Hydrophilic Transition

The pH-responsive release of drugs was owing to the transition of tertiary amine groups from hydrophobic to hydrophilic and the subsequent dissociation of structure. Zhang et al. designed a 4-diethylaminophenyl isothiocyanate. *(DAITC)-modified generation-five polyamidoamine (PAMAM) dendrimer (GDA) for delivering protein (25)

Acid-Labile Bond Cleavage

The acid-labile imine linkage in an acidic environment has also been used as an acidsensitive responsive bond for nano drug- loaded systems (25). In 2017, Ding et al. fabricated dextran-doxorubicin (Dex-DOX) nanoparticles based on imine linkage (26). Specifically, the hydroxyl groups on dextran were oxidized to aldehydes before being linked with DOX via imine linkage. The conjugate could self-assemble into uniform nanoparticles in an aqueous solution. The results proved that Dex-DOX could significantly improve cancer cellular uptake and enhance antitumor efficacy for B16-F10-bearing mice with excellent therapeutic safety (Figure 3). (27)

ROS-Responsive Nanocarriers

The higher level of ROS in cancer cells could also be used for the design and development of srNPs to enhance drug release at specific sites. In the design of ROS- responsive NDDS, the most commonly used groups are boric acid esters (28), thioketals, thioethers (29) and so on. A boric acid ester bond has been proven to be able to undergo ROS-induced degradation and its application in different fields has increased recently.

Temperature-sensitive nanoparticles

Temperature-sensitive nanoparticles are used for simultaneous hyperthermia- and temperature-triggered drug delivery. Magnetic nanoparticles encapsulated within thermosensitive polymeric nanoparticles and thermosensitive lipid nanovesicles can cause hyperthermia followed by a temperaturedependant release of encapsulated drugs, when exposed to an alternating magnetic field. Most of the literature using combined thermochemotherapy revolves around thermosensitive liposomes or polymeric nanoparticle using dipalmitoyl/distearoylphosphatidylcholine or poly(N-isopropylacrylamide), respectively, along with magnetic nanoparticles predominantly formed of iron oxides (30)

Acid-based changes

pH-sensitive nanoparticles are made of synthetic polymers and of nonlamellar phospholipids that release their cargo due to a phase transition of the carrier in the presence of acidic environments. Recently, some other nanomaterials have also been proposed for pH sensitivity; for example, mesoporous pH- sensitive silica nanoparticles that respond to the acidic pH of endosomes after endocytosis showed enhanced effects of chemotherapeutic
agents in drug-resistant cancers (31)

Enzymatic Cleavage

Enzyme-sensitive nanoparticles are another attractive option where the presence of enzymes that are overexpressed at the diseased sites is responsible for the increased leakage of drugs at the target site. Proteases are overexpressed in tumors and are often present at the sites of angiogenesis and at the invasive front of cancers, making them more accessible to nanoparticles by enhanced permeation and retention strategies. Proteases can act as triggers that can be exploited to expose an otherwise hidden surface of the nanoparticles such that the nanoparticles are inactive in the absence of the enzyme and become biologically active on exposure of the underlying surface in the presence of the enzyme (12). To avoid elimination by clearance organs (i.e., liver, kidneys, and spleen), the hydrodynamic size of

the nanoparticle (combined size of the core and coating) should remain small. The reticuloendothelial system (RES) readily takes up materials greater than 100 nm. Also, the basal lamina of the kidneys has pores of approximately 10 nm, so materials larger than this will not be filtered out of the blood. SPIONs with hydrodynamic sizes between 10 and 100 nm show greatly reduced liver and kidney uptake so are given the greatest opportunity to specifically interact with target cells (13).

FACTORS INFLUENCING NANOMATERIAL-CELL INTERACTIONS

There are numerous nanomaterial characteristics that influence their interactions with cells and cellular components. Key factors include the chemical nature of the nanomaterial, particle size, shape, texture, rigidity, charge, functional groups, and hydrophobicity/hydrophilicity. Additionally, phagocytosis and macropinocytosis are important pathways for nanoparticle internalization. Once inside the body, nanomaterials can form a "protein corona" by interacting with serum and extracellular matrix proteins, which can both mitigate toxicity and affect the nanomaterials' biological and physical properties. The chemistry of nanomaterials is critical, with biopolymer-based nanoparticles generally being more cell-friendly. Conversely, nanoparticles made from toxic heavy metals tend to be harmful. Specific chemical properties, such as elemental composition and functional groups, can influence systemic and local cellular responses, including solubility and ionization, which are crucial for understanding nanomaterial-induced toxicity. For example, highly soluble nanoparticles like zinc oxide (ZnO) exhibit higher cytotoxicity due to increased metal ion release. Functionalization of nanoparticles can modify these interactions, as seen with citrate- functionalized silver nanoparticles that exhibit specific cellular uptake and toxicity pathways. Minor changes in surface functionalization can also significantly impact cellular interactions and nanoparticle distribution within cells. (See Table 3). (32)

Control Release Nanoparticles Impressive on Cancer Therapy

Recent advance in nanotechnology is having a major impact on cancer therapy and diagnosis (34). At the center of this development is a variety of nanoparticles. These particles with a
diameter in the range of 50–400 nm can accomplish targeted delivery of anticancer drugs (33). A variety of nanoparticles have been developed and some of these are show in figure. Liposomes are lipid based vesicles and are widely used as drug delivery vehicles. Some are already used in clinics (35) . Polymer micelles are another type of nanoparticles that have been widely used and are evaluated in clinical trials. Dendrimers are formed by hyperbranched polymers. In addition, inorganic nanoparticles such as mesoporous silica nanoparticles, nanodiamonds and gold nanoparticles are used for drug delivery. Finally, engineered natural products that include engineered virus particles and vault nanoparticles have been developed. Because of their small size, these nanoparticles can take advantage of a leaky vasculature and accumulate in the tumor. This so-called EPR (enhanced permeability retention) effect appears to be particularly effective with tumor that has extensive vasculature (36). In addition to this passive targeting, positive targeting can be achieved by adding a targeting moiety on the surface of nanoparticles. Ligands or antibodies for receptors overexpressed on the surface of cancer cells can be used to accomplish positive targeting (Figure 4). (33)

How Nanoparticles Effects on Targeted Cancer Cells?

The utilization of nanotechnology in the diagnosis, treatment, and management of cancer has led to a whole new era. *NPs, either by active or passive targeting, augment the intracellular concentration of drugs while avoiding toxicity in the healthy tissue. *Targeted NPs can be designed and altered as either pH-sensitive or temperature-sensitive to establish and regulate the drug release. *pH-sensitive drug delivery system can deliver drugs within the acidic. *Similarly, the temperature sensitive NPs release the drugs in the target site due to changes in temperature brought in by sources like magnetic fields and ultrasound waves. *In addition, the “physicochemical characteristics” of NPs, such as shape, size, molecular mass, and surface chemistry, have a significant part in the targeted drug delivery system. *Further, NPs can be modified according to

the target and used to target a particular moiety (37)

Specialize in Delivering Tumor- Associated Antigens

Nanovaccines specialize in delivering "tumorassociated antigens" and "adjuvants" to antigenpresenting cells, such as dendritic cells (DCs). Moreover, these can also be employed as adjuvants to enhance "APC antigen presentation" and promote DC maturation that leads to the stimulation of cytotoxic T cells that have anti-tumor function. Liposomes, PLGA NPs, gold NPs are found to have the ability to deliver TAAs into DCs in the cytoplasm. Mesoporous silica, the most used inorganic NP, has exhibited an adjuvant role, leading to immune response stimulation. Artificial APCs interact with MHC-antigen complexes directly which binds to T cells. They also bind to costimulatory molecules that bind to costimulatory receptors leading to T cell activation. Targeting the immunosuppressed TME is yet another method of using NPs in immunotherapies. This is done by targeting essential cell types in TME such as "tumorassociated macrophages (TAMs)," regulatory T cells, and "myeloid-derived suppressor cells (MDSCs) (38).

DIFFERENT MODES OF NANOPARTICLES DRUG DELIVERY SYSTEM IN CANCER THERAPY

Innovative Stimuli-Responsive Nanoparticles for Controlled -Release And Enhanced Cancer Therapy

A myriad of drug delivery systems such as liposomes, micelles, polymers, and inorganic nanoparticles (NPs) have been developed for cancer therapy. Few, however, integrate multiple functionalities like specific delivery, high circulation stability, controllable release, and good biocompatibility in one system. We report two types of stimuli-responsive nonporous silica prodrug NPs for controlled release and combinatorial cancer therapy.

Anticancer drugs camptothecin (CPT) and Doxorubicin (DOX). They were encapsulated into silica matrices via glutathione (GSH)-responsive disulfide and pHresponsive hydrazone bonds, with NPs tunable in size from 50–200 nm. These NPs showed controlled release in GSH-rich or acidic environments, improving anticancer efficacy. When taken up by HeLa cells, they demonstrated remarkable combinatorial efficacy compared to free drug pairs. Thus, these stimuliresponsive silica prodrug NPs are promising for efficient cancer therapy (39).

Magnetic Nanoparticles for Application in Cancer Therapy

Biocompatible magnetic nanoparticles find wide applications in biomedical fields like magnetic resonance imaging, drug delivery, and hyperthermia. By inducing localized heating in tissues, they can selectively kill cancer cells above a critical temperature range. Iron oxidebased nanoparticles, when properly coated, are extensively researched for hyperthermia due to their biocompatibility. Optimizing their design is crucial to maximize heat generation. Factors like size, shape, solvent, and magnetic properties, along with the applied magnetic field's characteristics, influence their efficiency. The heating power rate is a key indicator of nanoparticle efficiency, as higher heating rates can reduce patient nanoparticle doses and duration of stay in the body. Hence, designing magnetic iron oxide nanoparticles with optimal properties remains a significant area of research (40).

Gold Nanoparticles in Cancer Therapy

The field of NP research presents exciting potential for biomedical applications. Together with an expanding knowledge base on the properties and effects of AuNPs, they are currently explored as potential tools for cancer therapy. Presently, exploiting AuNPs as sensitive probes in the detection and imaging of tumors for diagnostic purposes, delivery agents for the specific targeting of chemotherapeutic drugs to tumor cells, and enhancers in plasmonic photothermal therapy and radiation therapy for the eradication of tumor cells appear to show promise. In nanomedicine, the ultimate aim is to utilize NPs efficiently for the in vivo targeted killing of tumor cells with no or minimal side effects. However, even the concept of attaching ligands to the NPs so as to allow them

to hone to the tumor appears logical and simple but is in fact fraught with difficulties. In this light, NP research is still at its infancy since many factors remain to be optimized before the application of NPs in cancer therapy becomes a clinical reality (Figure 5). (41)

Nanoparticles Control Release Dosage Form Designed for Gene Therapy

Nanoparticles designed for gene therapy are generally cationic since the positively charged nanoparticles interact with negatively charged nucleic acids to form stable complexes. This is especially true for delivery of plasmid DNA which is relatively large (~100 nm) even when compacted (~10 nm). On the other hand, siRNA, which is small and rigid, is less restrictive on polymer coating (16). Once the nucleic acid bound SPION is internalized, DNA delivery requires access to the nucleus for successful transfection whereas siRNA only needs access to the cytoplasm to inhibit translation of mRNA. SPIONs coated with a copolymer of PEI, PEG, and chitosan (namely, NP-CP-PEI) are able to stably bind plasmid DNA, protect it from external molecules such as nucleases, and deliver it to the nucleus for transfection (32)

CONCLUSION

Nanoparticle-based drug delivery systems hold immense potential for revolutionizing cancer therapy by improving drug delivery efficiency, enhancing therapeutic efficacy, and minimizing adverse effects. The review underscores the importance of understanding nanoparticle properties and their interactions with biological systems to optimize therapeutic outcomes. Various types of nanoparticles, including liposomes, polymer micelles, dendrimers, and inorganic nanoparticles, offer versatile platforms for targeted drug delivery and controlled release. Moreover, magnetic nanoparticles and gold nanoparticles show promise in hyperthermia, targeted drug delivery, and gene therapy applications. However, further research is needed to address challenges such as optimization of nanoparticle design, targeting strategies, and clinical translation.

LIMITATIONS

This systematic review has several limitations. The literature survey is limited to articles published from 2007 to 2022, potentially excluding relevant studies published before or after this timeframe. Additionally, the selection of articles may introduce bias, and the review may not cover all advancements in nanoparticle-based drug delivery for cancer therapy. Moreover, while the review discusses various types of nanoparticles and their potential applications, it may not provide an exhaustive overview of all nanoparticle formulations and their therapeutic outcomes. Future research should aim to address these limitations and further explore the potential of nanoparticle-based drug delivery systems in cancer therapy.

Table 1: Types Of Novel Drug And Their Quality Eveidence

Types of Novel Drug	Study Year	First Author Name	Study Design	Sub-Types Targeted	Options	Quality of Evidence
Chitosan nanoparticleba sed system	2022	Yee Kuen, C.	Review	Lung cancer	Controlled release system	High (Review article)
Biopolymer nanoparticle production	2014	Hudson , D.	Review	General biopharma ce uticals	Controlled release	High (Review article)
Polysaccharide nanoparticles	2020	Bianche ra , A.	Review	Oral drug delivery	Drug–polymer and interpolyme r	High (Review article)

					interactions	
Nanomedicine based on nanoparticles	2015	Krukemey er, M. G.	Review	Various uses	Historical and potential uses	Moderate (Review article)
Magnetic nanoparticles	2011	Lee, J. H.	Experi me ntal study	Cancer therapy	Magnetic nanoparticl es	Moderate (Experimen tal study)
pH-sensitive mesoporous silica nanoparticles	2011	Huang, I. P.	Experi me ntal study	Chemothe rap y	pH-sensitive	Moderate (Experimen tal study)
Protease-triggered unveiling	2008	Harris, T. J.	Experi me ntal study	Bioactive nanopartic les	Proteasetri ggered	Moderate (Experimen tal study)
Nano-sized particles as imaging agents	2008	Longmire, M.	Experi me ntal study	Imaging	Nano-sized particles	Moderate (Experimen tal study)
Nanotechnolog ical carriers for chemotherapy	2015	Estanqueir o, M.	Review	Cancer	Nanotechn olo gical carriers	High (Review article)
Nanoparticle drug formulations	2014	Poon, W.	Review	Cancer	Diagnosis and treatment	High (Review article)
Multifunctiona l nanoparticles	2015	Raju, G. S. R.	Review	Cancer	Therapeuti cs	High (Review article)
Enhanced permeability and retention (EPR) effect	2001	Maeda, H.	Review	Cancer	Macromol ecu lar drug targeting	High (Review article)
PLGA-based nanoparticles	2018	Rezvantal ab, S.	Review	Cancer	PLGA-based nanoparticl es	High (Review article)
Nanoparticles for cancer therapy	2021	Gavas, S.	Review	Cancer	General progress and challenges	High (Review article)
Glutathione-and pHresponsive silica nanoparticles	2015	Xu, Z.	Experi me ntal study	Cancer therapy	Glutathion e and pHresponsi ve	Moderate (Experimen tal study)
Gold nanoparticles	2011	Lim, Z. Z. J.	Review	Cancer	Gold nanoparticl es	High (Review article)

Curcumin nanoparticles	2015	Zhang, J.	Experi me ntal study	Cancer therapy	Curcumin nanoparticl es	Moderate (Experimen tal study)
Types of Novel Drug	Study Year	First Author Name	Study Design	Sub-Types Targeted	Options	Quality of Evidence
Chitosan nanoparticleba sed system	2022	Yee Kuen, C.	Review	Lung cancer	Controlled release system	High (Review article)
Nanoparticles in drug delivery	2022	Afzal, O.	Review	Various	Therapeuti c application s	High (Review article)
Role of nanoparticles	2010	Sivasanka r, M.	Review	Drug delivery systems	General overview	Moderate (Review article)
Targeting nanoparticles to cancer	2010	Wang, M.	Review	Cancer	Targeting strategies	High (Review article)
Nanoparticles for combination therapy	2016	Jadia, R.	Review	Cancer	Combinati on therapy	High (Review article)
Controlled-release oxycodone tablets	2011	Ravera, E.	Clinical study	Pain manageme nt	Transderm al and oral administrat ion	Moderate (Clinical study)
Sustained drug release from smart nanoparticles	2022	Bai, X.	Review	Cancer	Sustained release	High (Review article)
Drug release kinetics on therapeutic efficacy	2014	Sethi, M.	Experi me ntal study	Cancer	Release kinetics and efficacy	Moderate (Experimen tal study)
Kinetic modeling on drug release	2010, 1996	Dash, S.	Experi me ntal study	Controlled drug delivery systems	Kinetic modeling	Moderate (Experimen tal study)
Novel mathematical method	2000	Gohel, M.	Experi me ntal study	Drug release	Mathemati cal modeling	Moderate (Experimen tal study)
Nanoparticle design strategies	2017	Dai, Y.	Review	Cancer	Tumor microenvir on ment	High (Review article)
Global cancer statistics	2021	Sung, H.	Review	Cancer	Incidence and mortality	High (Review article)
Combinational strategy for chemotherapy	2018	Qin, S. Y.	Review	Cancer	Highperfor mance chemother	High (Review article)

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Tumor microenvironment	2012	Balkwill, F. R.	Review	Cancer	Tumor microenvir on ment	High (Review article)
Nanoparticles for tumor microenvironment	2017	Yang, S.	Review	Cancer	Tumor therapy	High (Review article)
pH-responsive polymer for protein delivery	2021	Zhang, S.	Experi me ntal study	Protein delivery	pH-responsive	Moderate (Experimental study)
Programmed nanococktail for targeting therapy	2017	Li, Y.	Experi me ntal study	Cancer	pH-responsive function	Moderate (Experimental study)
Polysaccharide doxorubicin conjugate	2017	Feng, X.	Experi me ntal study	Cancer therapy	Schiff base bond-linked	Moderate (Experimental study)
NIR-responsive ROS generating microgel	2019	Lee, J.	Experi me ntal study	Cancer therapy	ROS-triggered release	Moderate (Experimental study)
ROS-responsive polymeric conjugate	2019	Oddone, N.	Experi me ntal study	Cancer therapy	ROS-responsive	Moderate (Experimental study)
ROS-responsive nanoassembly	2019	Luo, C.	Experi me ntal study	Chemopho todynami c therapy	ROS-responsive	Moderate (Experimental study)
Light-activatable prodrug nanoplatform	2018	Yang, B.	Experi me ntal study	Chemopho todynami c therapy	ROS-responsive	Moderate (Experimental study)

Table 02: Kinetic Models and Control Release Dosage Form

Kinetic Model	Description	Application
Zero Order Model	Describes systems where the drug release rate is independent of its concentration, typically utilized in the design of oral controlled drug delivery systems.	Suitable for highly water-soluble drugs; utilized in three-layer matrix tablets for bimodal release profiles (12)
First Order Model	Describes release from systems where the release rate is concentration- dependent. It's one of the earliest equations expressing dissolution rate quantitatively.	Commonly used for pharmaceutical dosage forms containing water-soluble drugs; applicable in hydrophilic matrices

		(17)
Higuchi Model	Describes drug release from insoluble matrix systems as a square root of time dependent process based on Fickian diffusion.	Commonly applied in transdermal and matrix tablet systems with water-soluble drugs (18)
HixsonCrowell Model	Describes release from systems where there's a change in surface area and diameter of particles.	Useful in understanding drug release from particle-based formulations; applicable in composite dosage forms (19)
KorsmeyerPeppas Model	Describes release mechanisms from polymeric systems.	Widely used in pharmaceutical formulations employing polymeric matrices; characterization of release mechanisms (19)
Hopfenberg Model	Developed to compare drug release from surface eroding polymers where the surface area remains constant during the degradation process.	Valuable in studying drug release from optimized oil spheres; application in site-specific biphasic release kinetics (19)

Table 3: Ph Response on SRNPS In Cancer Therapy

Responsive moiety	**Nanoplatform**	**Cargos**	**Application**
PolyHis	Poly (Lactic acid)-b-PEG-b polyHis micelles	DOX	PH-dependent drug release
	Polymeric micelles constitute of two block co-polymers of poly(L-lactic acid)-b-PEG- bpoly(L-histidine)-TAT and polyHis-b-PEG	D0X	PH-dependent drug release and tumor targeted chemotherapy
	A mixed-micelle system composed of polyHis- cophenylalanine-b-poly(L-lactic acid)-b-PEG-folate	DOX	Reversal of multidrug resistance of cancer
	A mixture of polyHis /PEGfolate and poly(L-lactic acid)-bPEG-folate	DOX	Reversal of resistant MCF-7 tumor
	A micelle composed of polyHisb-PEG and poly(L-lactic acid)-bPEG-b-polyHis-biotin	DOX	Increase of endocytosis
Tertiary amine	mPEG/HCou-g-MPCL micelles	DOX	pH-sensetive drug delivery
	GDA/EGFP	EGFP	pH-responsive cytosolic protein delivery
Sulfonamide	DNA/PEI/poly (methyacyclolyl sulfadimethoxine)-b-PEG	DNA	Tumor specific drug delivery
	Oligomeric sulfonamidesincorporated	DNA	Enhancement of nucleic acid delivery

	poly(Llysine)/DNA		
Hydrazone	HPMA	DOX	pH-sensitive drug release
	HPMA	DOX β-sitosterol	pH-sensitive tumor chemotherapy
	HA-hyd-DOX	DOX	pH-dependent drug release and tumor targeted chemotherapy
Orthoester	PEG-b-PtNEA27/56/73	Nile Red	Acid-sensitive and thermoresponsive drug release
	PMAOE	DNA	pH-modulated release of gene
Imine	Dex-DOX	DOX	PH-sensitive tumor chemotherapy
Benzoic imine	Benzoic-imine-containing PEI-gmPEG	ICG	Acid-triggered photoinitiation release
Acetals	MSN-R848-OVAp	R848 AND OVA	Ph-sensitive tumor immunotherapy
	Ac-DEX	Pyrene	pH-dependent drug release
Phlip	HauNS-Phlip-Ce6	Ce6	Tumor targeted PTT/PDT
	MONs	DOX	Tumor targeted chemotherapy (22).

Fig 1: DATA SYNTHESIZED AND PRESENTED BY FOLLOWING DIAGRAM

IDENTIFICATION	54 evidence identified by database [2 from each source Critical Reviews in Biotechnology, Journal of Nanomedicine & Nanotechnology, International Journal of Research in Pharmaceutical and Biomedical Sciences, International Journal of Nanotechnologyand Nanomedicine. 26 from Google Scholar	16 evidence identified byother sources; 02 from PharmacologicalResearch 02 from professional association websites
SCREENING	46 evidences remained after removal of duplicates [06 evidences collected from google schooler; 04 evidence was duplication from pharmacological research	
ELIGIBILITY	49 evidences screened	09 evidences excluded due to incompleteinformation
	41 full text evidence assessment foreligibility	19 full text evidence excluded due to non-eligibility
INCLUDED	41 evidence identified by database [2 f rom each source Critical Reviews in Biotechnology,Journal of Nanomedicine & Nanotechnology, International Journal of Research in Pharmaceutical and Biomedical Sciences, International Journal of Nanotechnology and Nanomedicine. 26 from Google Scholar. 16 evidence identified by other sources; 02 from Pharmacological Research 02 from professional association websites	

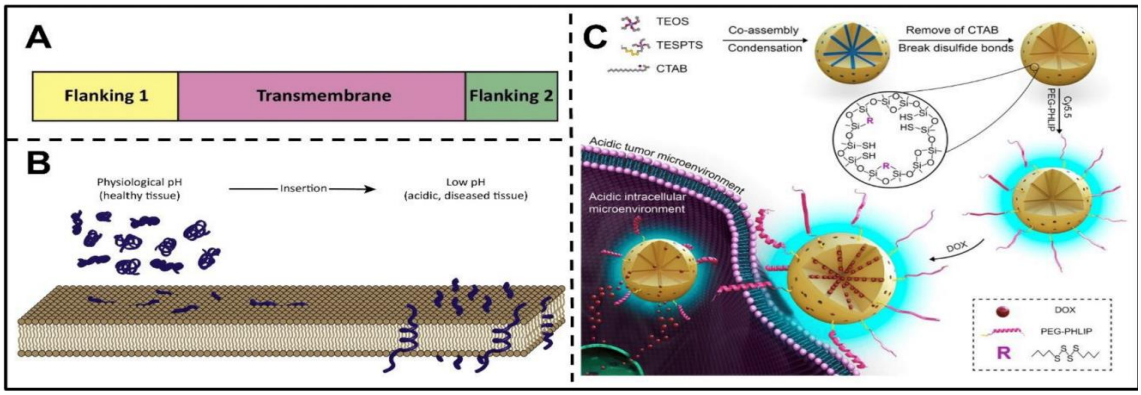

Fig 3. Schematic representing structure and pHsensitive transmembrane mechanism of pHLIP. (A) The main features of three sequences of pHLIP. (B) Schematic model of membrane interaction at physiological pH and insertion at low pH of pHLIP. Reproduced with permission. Copyright 2017, Elsevier. (C) Preparation of pHLIP- modified MONs and their targeting cancer therapy by pH-triggered transmembrane behavior. Reproduced with permission. Copyright 2017, American Chemical Society. (27)

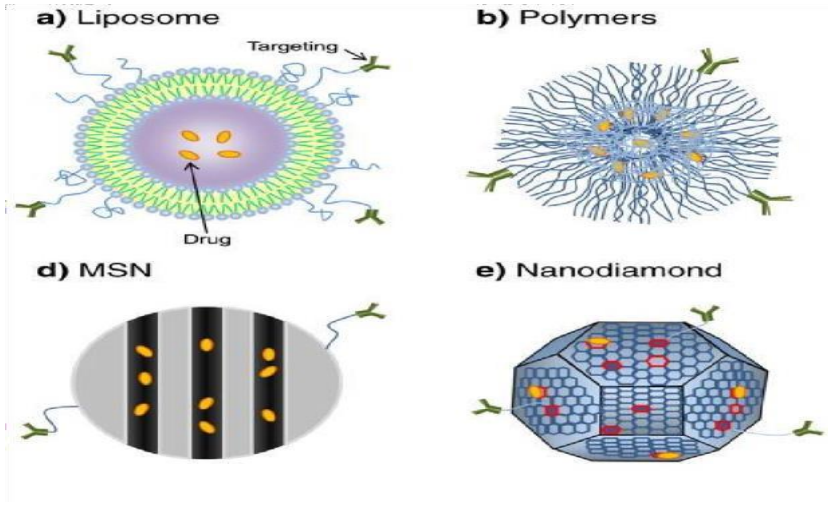

Fig 4: Ligands or antibodies for receptors overexpressed on the surface of cancer cells can be used to accomplish positivetargeting (33)

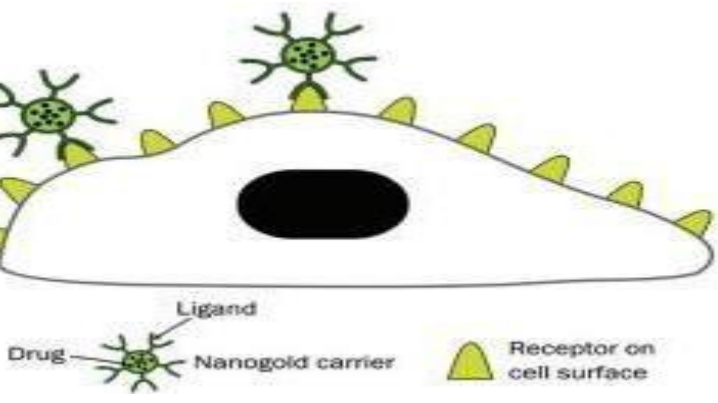

Fig 5: Gold nanoparticles in cancer therapy (41)

REFERENCE

1. Yee Kuen C, Masarudin MJJM. Chitosan nanoparticle-based system: A new insight into the promising controlled release system for lung cancer treatment. 2022;27(2):473.
2. Hudson D, Margaritis AJCrib. Biopolymer nanoparticle production for controlled release of biopharmaceuticals. 2014;34(2):161-79.
3. Bianchera A, Bettini RJEOoDD. Polysaccharide nanoparticles for oral controlled drug delivery: The role of drug–polymer and interpolymer interactions. 2020;17(10):1345-59.
4. Krukemeyer M, Krenn V, Huebner F, Wagner W, Resch RJJNN. History and possible uses of nanomedicine based on nanoparticles and nanotechnological progress. 2015;6(6):336.
5. Wang M, Thanou MJPr. Targeting nanoparticles to cancer. 2010;62(2):90-9.
6. Afzal O, Altamimi AS, Nadeem MS, Alzarea SI, Almalki WH, Tariq A, et al. Nanoparticles in drug delivery: From history to therapeutic applications. 2022;12(24):4494.
7. Jadia R, Scandore C, Rai PJIjon, nanomedicine. Nanoparticles for effective combination therapy of cancer. 2016;1(1).
8. Ravera E, Di Santo S, Bosco R, Arboscello C, Chiarlone RJAc, research e. Controlled-release oxycodone tablets after transdermal-based opioid therapy in patients with cancer and non-cancer pain. 2011;23:328-32.
9. Bai X, Smith ZL, Wang Y, Butterworth S, Tirella AJM. Sustained drug release from smart nanoparticles in cancer therapy: a comprehensive review. 2022;13(10):1623.
10. Imran SM, Shao GN, Kim H. https://www. sciencedirect. com/science/article/abs/pii/S092633731500346X. 2016.
11. Sethi M, Sukumar R, Karve S, Werner ME, Wang EC, Moore DT, et al. Effect of drug release kinetics on nanoparticle therapeutic efficacy and toxicity. 2014;6(4):2321-7.
12. Dash S, Murthy PN, Nath L, Chowdhury PJAPP. Kinetic modeling on drug release from controlled drug delivery systems. 2010;67(3):217-23.
13. Mathiowitz EJ. Encyclopedia of controlled drug delivery. 1999.
14. Bravo SA, Lamas MC, Salomón CJJJPPS. In-vitro studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices. 2002;5(3):213-9.
15. Singh R, Lillard Jr JWJE, pathology m. Nanoparticle-based targeted drug delivery. 2009;86(3):215-23.
16. Weng J, Tong HH, Chow SFJP. In vitro release study of the polymeric drug nanoparticles: development and validation of a novel method. 2020;12(8):732.
17. Gohel MC, Panchal MK, Jogani VVJAP. Novel mathematical method for quantitative expression of deviation from the Higuchi model. 2000;1:43-8.
18. Dai Y, Xu C, Sun X, Chen XJCSR. Nanoparticle design strategies for enhanced anticancer therapy by exploiting the tumour microenvironment. 2017;46(12):3830-52.
19. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2021;71(3):209-49.
20. Qin S-Y, Cheng Y-J, Lei Q, Zhang A-Q, Zhang X-ZJB. Combinational strategy for high-performance cancer chemotherapy. 2018;171:178-97.
21. Balkwill FR, Capasso M, Hagemann TJJocs. The tumor microenvironment at a glance. 2012;125(23):5591-6.
22. Yang S, Gao HJPr. Nanoparticles for modulating tumor microenvironment to improve drug delivery and tumor therapy. 2017;126:97-108.
23. Zhang S, Lv J, Gao P, Feng Q, Wang H, Cheng YJNL. A pH-responsive phase-transition polymer with high serum stability in cytosolic protein delivery. 2021;21(18):7855-61.
24. Li Y, Song L, Lin J, Ma J, Pan Z, Zhang Y, et al. Programmed nanococktail based on pH-responsive function switch for self-synergistic tumor-targeting therapy. 2017;9(45):39127-42.
25. Feng X, Li D, Han J, Zhuang X, Ding JJMS, C E. Schiff base bond-linked polysaccharide–doxorubicin conjugate for upregulated cancer therapy. 2017;76:1121-8.
26. Lee J, Jenjob R, Davaa E, Yang S-GJJoCR. NIR-responsive ROS generating core and ROS-

triggered 5′-Deoxy-5-fluorocytidine releasing shell structured water-swelling microgel for locoregional combination cancer therapy. 2019;305:120-9.
27. Oddone N, Pederzoli F, Duskey JT, De Benedictis CA, Grabrucker AM, Forni F, et al. ROS-responsive "smart" polymeric conjugate: Synthesis, characterization and proof-of-concept study. 2019;570:118655.
28. Luo C, Sun B, Wang C, Zhang X, Chen Y, Chen Q, et al. Self-facilitated ROS-responsive nanoassembly of heterotypic dimer for synergistic chemo-photodynamic therapy. 2019;302:79-89.
29. Lee J-H, Jang J-t, Choi J-s, Moon SH, Noh S-h, Kim J-w, et al. Exchange-coupled magnetic nanoparticles for efficient heat induction. 2011;6(7):418-22.
30. Huang I-P, Sun S-P, Cheng S-H, Lee C-H, Wu C-Y, Yang C-S, et al. Enhanced chemotherapy of cancer using pH-sensitive mesoporous silica nanoparticles to antagonize P-glycoprotein–mediated drug resistance. 2011;10(5):761-9.
31. Libo Y, Reza FJJPS. Pharmacokinetic profiles of two tablet formulations of Piroxicam. 1996;85:170-6.
32. Augustine R, Hasan A, Primavera R, Wilson RJ, Thakor AS, Kevadiya BDJMTC. Cellular uptake and retention of nanoparticles: Insights on particle properties and interaction with cellular components. 2020;25:101692.
33. Maeda HJAier. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. 2001;41(1):189-207.
34. Poon W, Zhang X, Nadeau JJCRiO. Nanoparticle drug formulations for cancer diagnosis and treatment. 2014;19(3-4).
35. Raju GSR, Benton L, Pavitra E, Yu JSJCc. Multifunctional nanoparticles: recent progress in cancer therapeutics. 2015;51(68):13248-59.
36. Rezvantalab S, Drude NI, Moraveji MK, Güvener N, Koons EK, Shi Y, et al. PLGA-based nanoparticles in cancer treatment. 2018;9:1260.
37. Gavas S, Quazi S, Karpiński TMJNrl. Nanoparticles for cancer therapy: current progress and challenges. 2021;16(1):173.
38. Xu Z, Liu S, Kang Y, Wang MJN. Glutathione-and pH-responsive nonporous silica prodrug nanoparticles for controlled release and cancer therapy. 2015;7(13):5859-68.
39. Rivas J, Bañobre-López M, Piñeiro-Redondo Y, Rivas B, López-Quintela MJJoM, Materials M. Magnetic nanoparticles for application in cancer therapy. 2012;324(21):3499-502.
40. Lim Z-ZJ, Li J-EJ, Ng C-T, Yung L-YL, Bay B-HJAPS. Gold nanoparticles in cancer therapy. 2011;32(8):983-90.
41. Zhang J, Li S, An F-F, Liu J, Jin S, Zhang J-C, et al. Self-carried curcumin nanoparticles for in vitro and in vivo cancer therapy with real-time monitoring of drug release. 2015;7(32):13503-10.