RESEARCH PAPER

Design And Chemical Characterisation Of Ph-Responsive Polymeric Nanocarriers For Targeted Anticancer Drug Delivery

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Abstract

Polymeric nanocarriers is gaining an emerging spotlight in present-day treatment for cancer owing to their ability to enhance effectiveness by drug delivery through increasing stability and aiding targeted delivery of therapeutic agents while also providing controlled release of therapeutic agents. pH-responsive polymeric nanocarriers have attracted much interest due to the potential that they offer to take advantage of the acidic conditions that are present in tumour tissues for more selective delivery of therapeutic agents. These systems are used to concentrate anticancer drugs at the site of the disease and downregulate the exposure to healthy tissues, thus improving the efficiency of the anticancer treatment and decreasing the adverse effects. This review is concerned with the latest advances in the development of pH-sensitive polymeric nanocarriers for targeted anticancer therapy. Emphasis is laid on their design principles, synthesis methods and chemical characterisation techniques. Previous research findings related to polymeric nanocarrier systems, fabrication approaches, drug loading methods as well as pH-triggered release mechanisms were examined. Common preparation techniques such as nanoprecipitation, emulsion solvent evaporation, and self-assembly are considered alongside emerging fabrication strategies, including microfluidic-based synthesis and layer-by-layer assembly methods. Studies have demonstrated that pH-responsive nanocarriers can achieve higher drug encapsulation efficiency, improved stability, and regulated drug release under acidic tumour conditions. Drug release can occur through mechanisms such as the cleavage of acid-sensitive bonds or swelling of polymer matrices caused by protonation of functional groups. Moreover, the development of multifunctional nanocarriers that combine therapeutic delivery with imaging, photothermal therapy, or photodynamic therapy has opened new opportunities for theranostic applications. Overall, polymeric nanocarriers represent a promising platform for targeted cancer treatment. Continued advances in polymer chemistry, nanofabrication technologies, and multifunctional system design are expected to further enhance their clinical potential. Future work should focus on improving scalability, ensuring long-term safety, and facilitating the successful translation of these systems into clinical practice.

Keywords: Anticancer Drug Delivery, Nanocarriers, Ph-Responsive Polymers, Polymeric Nanoparticles, Targeted Therapy

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Introduction

Cancer is a arising health concern and is one of the leading causes of morbidity and mortality worldwide. Although great progress has been made in diagnostic methods and treatment strategies, effective management of cancer is still difficult because of the complexity of tumour biology and the limitations associated with traditional therapies. Chemotherapy is widely used in the treatment of different types of cancer; however, conventional chemotherapeutic drugs generally have poor selectivity towards cancer cells, rapid clearance from the body, low bioavailability, and significant toxicity to healthy tissues. These drawbacks make the treatment less effective and often cause severe adverse effects, which in the end, affect the well-being and treatment effects for patients. For this reason, the development of advanced drug delivery systems that can increase the precision and effectiveness of anticancer

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*Author for Correspondence: dr.sarikabajpai@gmail.com therapies has emerged as an important area of pharmaceutical and biomedical research[1].

Nanotechnology-based drug delivery platforms have been developed as promising tools for improving the pharmacokinetic and pharmacodynamic behaviour of anticancer drugs. Nanocarriers have been seen to have several advantages, including increased solubility of the drug, extended circulation time in the blood, increased drug stability and preferred accumulation at tumour sites. The small size of nanoparticles enables them to exploit a phenomenon known as enhanced permeability and retention or EPR effect in which nanoparticles concentrate within tumour tissues due to irregular vascular structures and poor lymphatic drainage[2]. This passive targeting property has been exploited on a large scale in the development of nanomedicine for cancer treatment. Besides passive targeting, the nanocarrier surface can also be functionalized with targeting ligands identifying specific receptors on cancer cells, active targeting, and an improved outcome of drug delivery and therapy.

Among the different types of nanocarrier systems that have been studied for anticancer therapy, polymeric nanocarriers have attracted a lot of attention owing to their versatile physicochemical properties and flexible structure design. Polymeric materials can be designed to form a variety of nanostructures including polymeric nanoparticles, micelles, dendrimers, and nanogels that are able to encapsulate therapeutic molecules and protect them from premature degradation. These systems are capable of delivering both hydrophilic and hydrophobic drugs, and can be designed to give sustained or controlled release of drugs. Moreover, polymeric nanocarriers may be functionalized with specific chemical groups or targeting ligands to improve their stability, cellular internalization and tumour-targeting ability. Recent studies have given emphasis on the efficacy of polymer-functionalized nanocarriers in the improvement of intracellular drug delivery and the overall treatment performance of anticancer drugs[3].

Stimuli-responsive drug delivery systems are a significant development of nanomedicine because they permit the controlled release of drugs according to some given biological or environmental stimulus. These stimuli can be both external, in the case of temperature, light or magnetic fields, or internal, for pH, enzyme activity or redox potential. Among these stimuli, pH-responsive systems have attracted major attention because of the difference of the pH between normal tissues and tumour microenvironments[4]. Tumour tissues typically possess a slightly acidic extracellular pH as compared to physiological conditions whereas intracellular compartments such as endosomes and lysosomes possess even lower pH values. These differences represent an opportunity for the design of smart nanocarriers suitable for the selective release of therapeutic agents in an acidic environment, which can enhance the accumulation of drugs within the cells of the tumour as well as decrease toxicity to the rest of the organism[5].

Recent progress in polymer chemistry has led to the development of a wide range of pH-responsive polymeric materials that have the ability to undergo structural or chemical changes in an acidic environment. Polymers such as poly(histidine), poly(acrylic acid), poly(beta amino esters) and various derivatives of natural polymers have been extensively studied with regard to their responsiveness against pH changes in the tumour microenvironment. Dimensions-lists of gradable polymers can be made to contain protonatable groups or acid-labile bonds, which can release a drug due to the acidic environment[5]. Several studies have reported the successful development of pH-sensitive polymeric nanocarriers for the delivery of anticancer drugs such as doxorubicin, methotrexate and 5-fluorouracil with enhanced therapeutic efficiency and decreased systemic toxicity[6].

In addition to the polymer design, for efficient nanocarrier systems, there is a need for thorough chemical and physicochemical characterisation in order to guarantee their stability, safety, and performance in biological environments. Similarly, methods of nanoparticle characterisation such as dynamic light scattering, transmission electron microscopy, scanning electron microscopy and zeta potential analyses are important to assess particle size, morphology, surface charge and colloidal stability. These parameters play a critical role in determining the biological behaviour of nanocarriers, such as circulation time, cellular uptake, and drug release characteristics[7].

Recent studies have also examined how to incorporate multifunctional components into the nanocarrier systems in order to further improve the therapeutic efficiency. Hybrid nanocarriers with magnetic nanoparticles, graphene oxide or other nanomaterials have shown increased drug loading capacity, targeted delivery and increased anticancer activity. These multifunctional systems can incorporate drug delivery with imaging or diagnostic capabilities, and can therefore be used for theranostics in cancer treatment. Such innovations reflect the fast-developing character of nanomedicine and the possibility to revolutionize cancer therapy by more accurate and efficient drug delivery methods[8].

Overall, the creation of pH-responsive polymeric nanocarriers is an interesting solution for the enhancement of targeted cancer drug delivery. Through the exploitation of acidic tumour microenvironment and the well-knit design strategies of polymers, these tumour-targeting systems can lead to improved drug accumulation in the tumour tissues with reduced toxicity in the host. It can be expected that continued progress in polymer chemistry, nanocarrier engineering and characterisation techniques will further enable the advancement and clinical usefulness of these systems to develop more effective and safer forms of cancer treatment[9].

Objectives of the Review

- To review recent developments in the design and development of pH-responsive polymeric nanocarriers for targeted anticancer drugs delivery.
- As well as the various applications for these nanoparticles, these can be used in different ways depending on the actual application.
- To assess the therapeutic potential, drug release mechanism and current challenges related to polymerase nanocarriers that are pH-responsive in cancer treatment

1. **Tumour Microenvironment and pH Variations Relevant to Drug Delivery**

The tumour micro-environment is a very important factor in determining the effectiveness of anticancer therapies and the delivery of drugs. Unlike normal tissues, the physiological and biochemical properties of tumour tissues are abnormal, such as irregularity of vascular structure, hypoxia, abnormal metabolic and acid extracellular environment, etc. These features are a result, primarily, of the high rate of growth of cancer cells which, with a high dependence on glycolysis for their metabolism, even in the presence of oxygen, is commonly called the Warburg effect10. This metabolic shift leads to the overproduction of lactic acid, which causes a drop of the pH value of the extracellular fluid in tumour tissues. Therefore, the extracellular pH level of the tumour environment is typically in the range of 6.5-6.8; the pH value of normal physiological tissues is close to 7.4. These differences in pH conditions are an important biological trigger that can be taken advantage of when designing responsive drug delivery systems for the selective release of therapeutic agents at tumour sites[11,12].

The acidic character of the tumour microenvironment is further extended to equivalent intra-compartments inside the cancer cells. Organelles that contain endosomes and lysosomes possess significantly lower pH values ranging typically from pH 4.5 to 6.0. These intracellular acidic environments are thought to play an important role in the intracellular trafficking and processing of NPs and drug carriers. When internalised by cancerous cells via endocytosis, for example, nanocarriers travel through these organelles that are rather acidic and hence provide the opportunity for the pH-sensitive systems to undergo a structural transformation leading to release of their therapeutic payloads. Exploiting such pH gradients has become an important strategy in the development of targeted drug delivery systems with a low premature release of the drug and a high drug concentration inside the cancer cells. Several nanocarrier systems such as metal organic framework nanoparticles or host-guest supramolecular system have been designed to respond to these pH variations in order to improve the targeted delivery to tumor tissues[7,10].

The exploitation of the tumour acidity as a stimulus for drug delivery has lead to a great number of research groups to develop pH-responsive nanocarriers in the recent years. These systems have been designed to be stable at physiological pH conditions but undergo structural modification, or the cleavage of bonds, in lower pH conditions. Such responses may include swelling of polymers or functional group protonation or detachment of acid sensitive linkers and lead to the initiation of controlled drug release[13]. This strategy has the major advantage of optimising the therapeutic index of anticancer drugs by enhancing the accumulation of anticancer drug at the site of the tumour and decreasing the exposure of the healthy tissues elsewhere. In addition, pH sensitive systems can be combined with other targeting approaches as for example ligand mediated targeting or multifunctional nanocarrier systems for further improving the efficiency of treatment. Comprehensive reviews on stimulus-responsive nanocarriers have demonstrated the significance of pH gradients in the design of smart drug delivery systems and also their potential in the enhancement of the selectivity and efficacy of cancer treatments[14].

2. Polymeric Nanocarriers in Anticancer Drug Delivery Systems

Polymeric nanocarriers have become one of the most versatile platforms for anticancer drug delivery thanks to their tunable physicochemical properties, biocompatibility and the controlled drug release offered by such smart formulation. These nanocarriers are usually made using natural polymers, synthetic polymers or a mixture of the two, and offer researchers the possibility to design specific structural and functional systems[15]. Polymeric nanocarriers are able to encapsulate therapeutic molecules into their matrix or link them by chemical conjugation that ensures protection of drugs from premature degradation and higher stability in biological environments. These carriers can also enhance the solubility of hydrophobic drugs and help transport these drugs across biological barriers, increasing the overall efficiency of their treatment in cancer treatment[16].

Solid colloidal systems known as polymeric nanoparticles possess the capacity to encapsulate and to release pharmaceuticals over time. Hydrophobic drugs may be solubilized by polymeric micelles, which are composed of amphiphilic block copolymers that self-assemble in an aqueous medium to form core-shell structures[17]. Dendrimers have the ability to control the drug loading and surface functionalization precisely because they are highly branched macromolecules with unique structure and trends. Conversely, nanogels are networks of crosslinked polymers that can absorb a lot of water without losing their structural integrity[18].

Recent developments have also been made to introduce multifunctional properties into polymeric nanocarriers to improve their therapeutic performance. For instance, Carretero-Flores & Laspedes stated that "Silk fibroin-based nanocarriers have been demoning the potential of combining photothermal therapy and chemotherapy combination therapies to synergically combat anticancer"-this shows that these nanocarriers have the potential to combine photothermal therapy with chemotherapy to greater cancer-fighting effects. Similarly, polymeric nanocarriers intended to be used in photodynamic therapy or in imaging, have shown promise as theranostics in cancer treatment[19]. The multifunctional systems enable simultaneous delivery of a drug, imaging, and tracking the therapy which offer new prospects to individualized medicine and accurate oncological therapy. The joining of polymer chemistry and nanotechnology keeps opening the doors to the potential of polymeric nanocarriers in targeted anticancer drug delivery systems[11.20].

3. Design of pH-Sensitive Polymeric Nanocarriers Strategies

The design of pH-responsive polymeric nanocarriers is based on the introduction of functional groups or chemical bonds that are sensitive to changes in the environmental pH. These are systems that are designed to be stable under normal physiological conditions but transform structurally under the acidic conditions of tumors[12]. One of the common approaches used is the addition of acid-sensitive linkers; these linkers swell under acid, and this causes the release of encapsulated drugs. Such design strategies enable to precisely control of the release of the drug, so that the drug therapeutic agents are delivered to tumour tissues but not to the healthy organs[13].

Another design approach of importance is the use of protonatable polymers that experience conformational changes in the presence of acidic conditions. Polymers with amino groups or other ionizable functional groups may become protonated in an acidic environment, thus causing swelling or instability in the structure of the nanocarrier. This process helps in the release of the encapsulated drug at the desired location. For example, polymeric micelles and dendrimer-based carriers have been developed that respond to the change in pH between tumour tissues and intracellular compartments to achieve efficient drug carriers and efficient cellular uptake of these drugs. These systems often involve the use of targeting ligands that further enhance the selectivity of the drug delivery to the cancer cells[21].

Recent studies have also focused on the design of hybrid approaches that include pH responsiveness, but such hybrid designs include other stimuli-responsive mechanisms. Multifunctional nanocarriers that can respond to both pH and redox conditions have shown an improved drug release performance and enhanced therapeutic outcomes. These are advanced systems that, in many cases, integrate imaging capabilities or targeting moieties that allow precise monitoring of drug delivery processes[22]. Such multifunctional pH-responsive polymeric nanocarriers are a promising direction that could be followed to increase the efficiency of targeted anticancer therapy as well as to overcome limits in working with conventional drug delivery systems[18]. Different structural design strategies have been applied to improve the responsiveness and targeting ability of polymeric nanocarriers, as shown in Table 1.

Table 1: Design strategies employed in the development of pH-responsive polymeric nanocarriers

Design Strategy	Mechanism	Advantages	Reference
Acid-labile linker conjugation	Cleavage of hydrazone/imine bonds in an acidic tumour environment	Controlled and targeted drug release	12,13
Protonatable polymer groups	Protonation leads to swelling and drug diffusion	Enhanced intracellular drug delivery	14
Charge-conversion polymers	Surface charge changes in acidic pH	Improved cellular uptake	21
Targeted ligand functionalization	Binding with cancer cell receptors	Increased targeting efficiency	15,18
Multifunctional nanocarriers	Combination of pH response with imaging or therapy	Theranostic applications	22

4. Types of pH-Sensitive Polymers Used in Nanocarrier Fabrication

pH-sensitive polymers are an important component in the preparation of responsive nanocarriers, which release drugs under acidic conditions in tumours. These polymers have ionizable functional groups or acid-labile bonds that respond to the variation in environmental pH. One of the most widely studied classes of pH-sensitive polymers is that of poly(acrylic acid) and its derivatives. These polymers have carboxylic acid groups that result in protonation and deprotonation depending on the pH of the surrounding environment. At acidic pH levels, due to the protonation of these groups, the conformation of the polymers and their swelling behaviour change, which aids in the release of the drug from the nanocarrier system[22].

Another class of important pH-sensitive polymers are the poly(histidine) and poly(beta amino esters), which contain amino groups that can be protonated in an acidic environment. Protonation of these groups can interrupt the stability of polymeric assemblies such as micelles or nanoparticles, leading to the release of drugs. Chitosan and its derivatives have also been widely studied as pH-sensitive materials because they have natural biocompatibility as well as amino groups that respond to acidic conditions. These polymers are of special interest for biomedical applications as they make the combination of pH sensitivity and biodegradability possible with minimal toxicity[13].

Recent developments in polymer chemistry have made it possible to create multifunctional polymers that contain multiple sensitive components in one nanocarrier system. These polymers can contain targeting ligands, imaging agents, or other components that are sensitive to stimuli in order to improve the performance of the therapy. Hybrid polymeric systems containing natural and synthetic polymers have proven to show an improved drug loading capacity and controlled release characteristics. Such innovations in polymer design continue to broaden the variety of materials that can be used to make advanced pH-responsive nanocarriers to deliver anticancer drugs[23].

5. Methods of Synthesis and Fabrication of Polymeric Nanocarriers

The fabrication of polymeric nanocarriers involves several fabrication methods that allow one to control the particle size, morphology, and drug loading capacity. One often adopted method is that of nanoprecipitation, wherein polymers and drugs are taken up in an organic solvent, and the same is added to an aqueous phase under controlled conditions. This process leads to the formation of nanoparticles by a process of rapid diffusion of solvents and precipitation of polymers. Nanoprecipitation has advantages such as simplicity, reproducibility, and producing nanoparticles of narrow size distributions[21,23].

Another type of widely used fabrication method is the emulsion solvent evaporation technique, which consists of an oil-in-water emulsion formation followed by the elimination of a solvent to obtain polymeric nanoparticles. This method is especially useful in encapsulating the hydrophobic drugs in polymer matrices. Self-assembly methods have also been commonly used in the preparation of polymeric micelles and other nanostructures. Amphiphilic block copolymers can spontaneously assemble into micellar structures under aqueous environments with a hydrophobic core able to encapsulate drugs and a hydrophilic shell able to stabilise the nanocarrier in biological fluids[22].

Recent studies have also addressed advanced fabrication techniques, including advanced methods like the layer-by-layer technique, microfluidic synthesis and template-assisted methods to achieve highly uniform nano-carriers. These techniques provide higher control over the nanocarrier architecture, as well as the possibility of including several functional single components in a system. The ongoing search for novel fabrication techniques is critical to the further advancement of the scalability, reproducibility and clinical feasibility of polymeric nanocarriers in anticancer drug delivery[24]. The fabrication process of polymeric nanocarriers is shown in Figure 1.

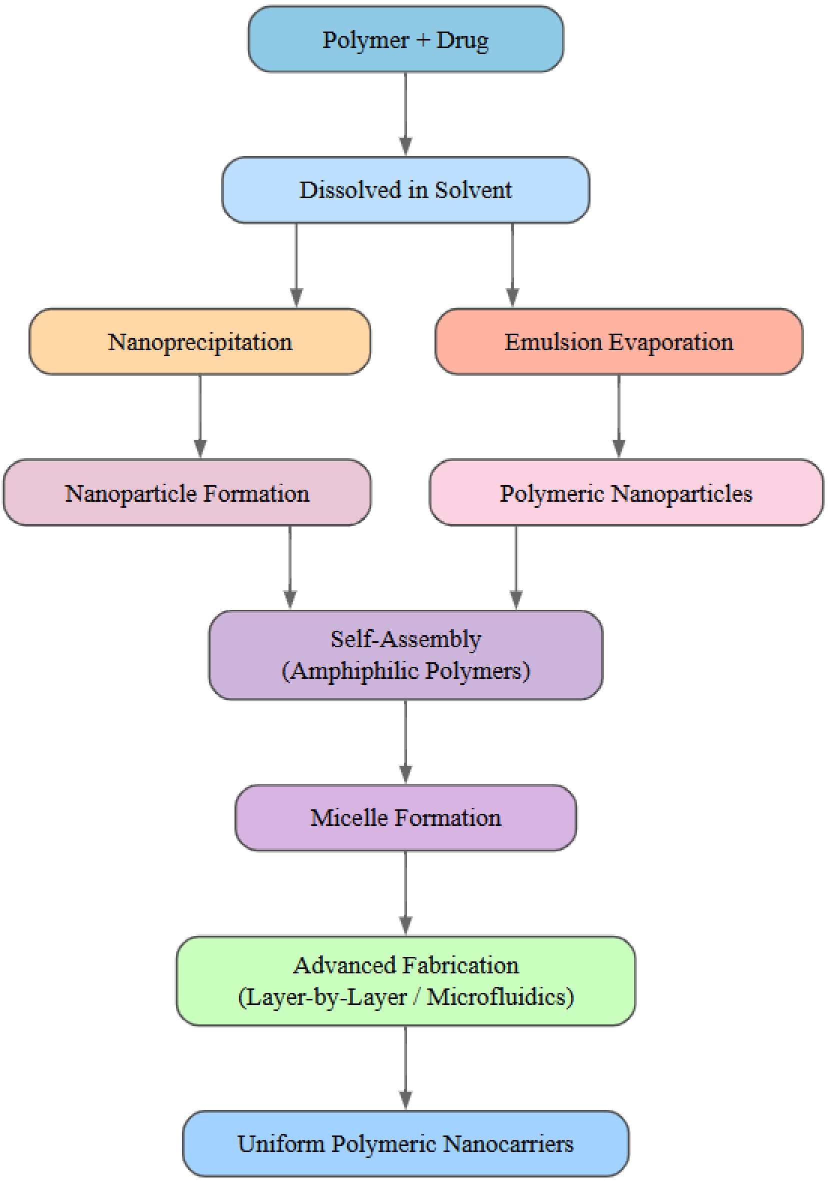

Figure 1: Fabrication pathways of polymeric nanocarriers

6. Chemical and Physicochemical Characterisation Techniques

Chemical characterisation is a very important step in the methods for the confirmation the structure and composition of polymeric nanocarriers. Methods such as Fourier transform infrared spectroscopy, nuclear magnetic resonance spectroscopy are generally used in the determination of functional groups, as well as the confirmation of polymer formation. These technique of analysis provide extensive data about the chemical structure of the polymer and confirm the presence of pH sensitive functional groups that were introduced during the creation of the polymer. Gel permeation chromatography is another important technique that is used to find the molecular weight distribution of polymers, since this will affect their physicochemical properties as well as their delivery performance[25].

Physicochemical characterisation is also equally important in the case of the evaluation of the properties of the nanocarriers themselves. Dynamic light scattering is a common technique for determining the size of nanoparticles and polydispersity index, important parameters in determining circulation time and cellular uptake[9,12]. Zeta potential measurements are used to determine surface charge, which affects the stability of nanoparticles and their interactions with biological membranes[25]. Additional characterisation techniques, such as differential scanning calorimetry and thermogravimetric analysis, are used to assess the thermal stability of polymeric nanocarriers and drug-polymer interactions. These methods give insights into the physical state. When assessing the characteristics of the nanocarriers themselves, physicochemical characterisation is equally crucial. A popular technique for estimating nanoparticle size and polydispersity index—two crucial factors in figuring out circulation time and cellular uptake—is dynamic light scattering.

Surface charge that influences the stability of nanoparticles and their interactions with biological membranes is measured using zeta potential[25]. encapsulated drugs and determine whether drugs are present in crystalline or amorphous states within the matrix of nanocarriers. Comprehensive characterisation guarantees the reproducibility and reliability of polymeric nanocarriers and plays an important role in the optimisation of their performance for targeted anticancer drug delivery[26].

7. Drug Loading Schemes and Encapsulation Effectiveness.

Drug loading is the amount of drug that is loaded inside the nanocarrier compared to the total mass of the carrier system, whereas the encapsulation efficiency is the percentage of originally used drug that is successfully entrapped inside the nanocarrier during the fabrication process. These parameters are a huge factor in determining the therapeutic effectiveness of the drug delivery system, since they affect dosage requirements, release kinetics and overall treatment efficiency[27]. Higher drug loading capacity means a higher amount of therapeutic agent can be delivered to the site of tumour action, which means lower frequency of administration and fewer systemic side effects. Consequently, different formulation strategies have been devised to achieve drug loading and encapsulation efficiency optimisation in polymeric nanocarriers for anticancer therapy[28].

Among the different approaches, physical encapsulation is one of the most widely used techniques of incorporating drugs in polymeric nanoparticles as well as micellar systems. In this method, there are two different ways in which drug molecules are entrapped in the hydrophobic core or dispersed in the polymer matrix during the formation of nanoparticles. This technique is especially amenable to hydrophobic anticancer drugs, as the hydrophobic environment of polymeric micelles/nanoparticles constitutes a favourable environment for drug retention[29]. Another more important strategy is via chemical conjugation, in which drug molecules are covalently attached by cleavable linkages to polymer chains. These bonds can be engineered to have a specific response to a given environmental trigger, such as acidic pH, enzymatic activity, or redox conditions, in order to allow for the control and targeted release of drugs. In contrast, electrostatic interactions, hydrogen bonding, or van der Waals forces between drug molecules and the polymer surface are the main mechanisms in loading methods based on adsorption. Each of these approaches has different advantages based on the physicochemical characteristics of the drug as well as the desired release profile[30].

Hybrid nanocarrier systems that involve conjugating polymeric materials with inorganic elements such as metal-organic frameworks, mesoporous materials or nanocomposites have shown a much higher drug loading efficiency. These hybrid configurations are available that offer high surface area and porosity that help in incorporating large amounts of drugs and control of release characteristics. In addition, multifunctional polymers with the ability to interact with drug molecules by various binding mechanisms have been designed to further enhance the loading efficiency[31]. Optimising these loading strategies of drugs is the key to maximising the therapeutic potential of polymeric nanocarriers and to efficient delivery of anticancer drugs to tumour tissues. Various drug loading techniques and their corresponding advantages are summarised in Table 2.

Table 2: Drug loading approaches and encapsulation strategies

Loading Strategy	Description	Advantages	Reference
Physical encapsulation	Drug trapped within the polymer matrix or core	Simple fabrication and high compatibility	19
Chemical conjugation	polymer chain attached by a covalent bond to drugs	Controlled release	13
Electrostatic adsorption	Ionic bond association between the drug and the polymer	Improved drug stability	25
Hybrid nanocarrier loading	Drug incorporated within composite materials	Higher loading efficiency	31
Self-assembled micelle loading	A hydrophobic drug incorporated in the micelle core	Improved solubility of hydrophobic drugs	34

8. Mechanisms of pH-Triggered Drug Release in Polymeric Nanocarriers

The controlled release of drugs from pH-responsive polymeric nanocarriers is mainly affected by structural and physicochemical changes that occur in the nanocarrier when it is exposed to acidic environments. Tumour tissues and intracellular compartments, such as endosomes and lysosomes, usually have lower pH values than do normal physiological conditions. These acidic environments are acting as a trigger to activate the pH-sensitive systems in the nanocarriers to achieve the selective release of therapeutic agents at the desired target site[32]. One of the most used mechanisms is the cleavage of acid-sensitive chemical bonds linking drug molecules to polymer chains or maintaining the structural integrity of the nanocarrier system. These bonds, such as hydrazone, imine and acetal linkages, are stable in neutral physiological conditions but hydrolyse in an acidic environment. As a result, the degradation of these bonds causes the detachment and subsequent release of the encapsulated drug molecules specifically inside tumour tissues or intracellular compartments and thus minimising premature leakage of the drug during systemic circulation and enhancing therapeutic selectivity[33].

Another important mechanism responsible for pH triggered drug release is protonation induced swelling of polymer matrices. Many pH-responsive polymers contain ionizable functional groups such as amino or carboxyl groups, which can undergo protonation under acidic conditions. When these groups become protonated, there will be more electrostatic repulsion force between polymer chains, thus causing the polymer matrix to expand and absorb water[24,34]. This phenomenon of swelling increases the internal pores of the nanocarrier, which in turn increases the permeability of the system and makes the drug molecules diffuse in the biological environment. Such swelling-based release mechanisms often are seen in hydrogel-based nanocarriers, polymeric nanoparticles and polymeric micelles for pH-responsive drug delivery. These systems are especially beneficial since they allow slow and controlled drug diffusion, resulting in a sustained therapeutic effect with minimal toxicity to the rest of the body[34].

Recent development of nanotechnology has also resulted in the development of multifunctional pH-responsive nanocarriers that have multiple drug release mechanisms incorporated in a single delivery platform. Hybrid systems of polymer matrices with metal organic frameworks, inorganic nanomaterials or nanocomposites have shown higher drug delivery efficiencies. The acidic conditions can also simultaneously induce the structural degradation of the carrier material, as well as cause a rise in the diffusion of the drug by causing porous networks in these systems. Such dual or multi-stimuli release strategies allow for better control over the kinetics of drug release and provide better performance of the therapy under complex biological environments[16]. Furthermore, the addition of targeting ligands, imaging materials or photothermal agents into these nanocarriers enables the creation of theranostics platforms, which can simultaneously deliver drugs and provide a way of monitoring the drug's activity. Understanding these various pH-triggered release mechanisms is thus crucial for the design of highly efficient nanocarrier systems with the ability to deliver anticancer drugs with improved specificity, controlled release behavior and enhanced therapeutic results[35]. The pH-triggered drug release mechanism from polymeric nanocarriers is illustrated in Figure 2.

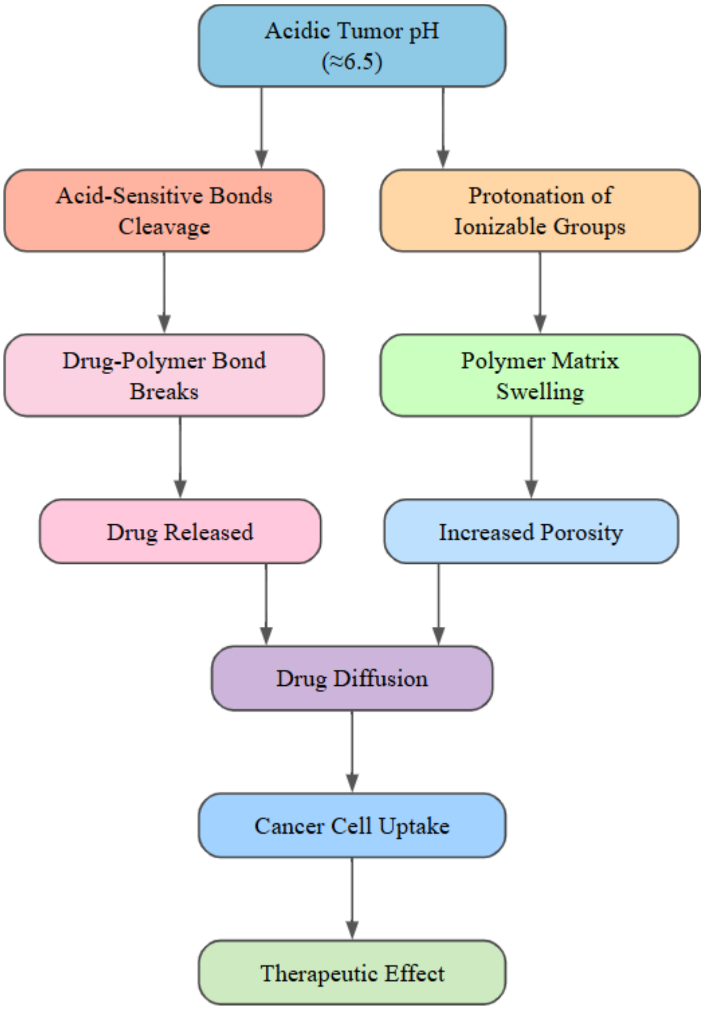

Figure 2: Mechanism of pH-responsive drug release from polymeric nanocarriers

9. Therapeutic Applications, Challenges, and Future Perspectives

pH-responsive polymeric nanocarriers have proven extremely useful in the improved therapeutic control of different types of cancers such as breast, lung and colorectal malignancies. These nanocarrier systems enhance the delivery efficiency of anticancer medications routinely used, such as doxorubicin, paclitaxel and methotrexate, by allowing a controlled and site-specific delivery of drug compounds in tumour tissues. The design of these carriers exploits the acidic tumour microenvironment that usually has lower pH values than the normal physiological conditions. This pH gradient is a stimulus and causes the release of encapsulated drugs from the nanocarrier system[36]. As a consequence, it is possible to have higher concentrations of therapeutic agents accumulated at the tumour site, with minimal exposure to healthy tissues. Such targeted drug delivery has a big benefit in terms of increasing treatment efficacy and decreasing systemic toxicity[37]. In addition, improved cellular uptake and enhanced cytotoxicity effect have been found when anticancer drugs are delivered from pH-responsive nanocarrier systems that further demonstrate their therapeutic potential in cancer treatment[38,39].

Despite these promising results, there remain a number of problems that limit the successful clinical translation of polymeric nanocarrier-based drug delivery systems. One of the major challenges is to manufacture nanocarriers on large scales and with reproducibility while ensuring the same physicochemical properties such as particle size, morphology and drug loading efficiency[40]. Long-term stability in storage and transport, though, is another important factor that must be addressed in order to ensure the reliability of these systems for clinical use. Moreover, relevant regulations on nanomedicine products are still complicated to be put into place and this may take a lot of preclinical and clinical testing to ensure that the safety, efficacy and quality levels are established[41]. The interaction of polymeric nanocarriers with biological systems also needs care and particular attention with respect to immune system responses, biodistribution patterns and possible toxicity. Addressing these challenges is fundamental to enable the successful clinical implementation of polymeric nanocarrier technologies[42].

In future is expected on the development of advanced multifunctional nanocarrier systems will incorporate therapeutic, diagnostic and imaging functionalities in one single platform[43]. The combination of nanotechnology and advanced materials science may allow for the development of smart nanocarriers that react to multiple types of biological stimuli. Such systems that are responsive to multiple stimuli may lead to better control over drug release and to better treatment outcomes[44]. Also, next-generation nanoparticle engineering methods and high-throughput screening methodologies are expected to speed up the discovery and optimisation of next-generation nanomedicine platforms. These developments are likely to bring in the future more precision, efficiency, and safety of administration of targeted cancer therapies[45]. Recent studies highlighting the therapeutic applications and performance of various nanocarrier systems across different cancer types are summarised in Table 3.

Table 3: Therapeutic applications in cancer treatment

Nanocarrier Platform	NDDS	Cancer Type	Key Outcome	Reference
Liposomal nanocarriers	Retinoic acid, docetaxel	Lung cancer	Improved cytotoxicity and cellular uptake	40
Hybrid liposome polymer systems	Curcumin, dexamethasone	Various cancers	Enhanced synergistic anticancer activity	38
Nanocomposite hydrogels	Curcumin	Skin cancer	Improved drug penetration and delivery	39
Nanostructured lipid carriers	Resveratrol	Glioma	Increased cellular uptake and cytotoxicity	44
Lipid nanoparticle systems	Anticancer drugs	Multiple cancers	Improved delivery pipeline development	45

10. Conclusion

pH-responsive polymeric nanocarriers are one of the important developments in anticancer drug delivery systems. The unique physicochemical features of polymer-based nanocarriers, such as biocompatibility, structural versatility, and controlled release ability of the drug, make them good platforms for improving the therapeutic efficiency of anticancer compounds. Various polymers and nanostructured systems have been successfully designed to respond to pH changes through processes such as protonation, swelling and acid-labile bond cleavage, which shows great potential for controlled and targeted drug delivery.

Extensive research has also underlined the relevance of chemical and physicochemical characterisation of the goals of guaranteeing the stability, reproducibility and effectiveness of these nanocarriers. Advanced fabrication techniques and multifunctional design strategies have also further expanded the capabilities of polymeric nanocarriers to provide improved drug loading efficiencies, enhanced cellular uptake and also combine functionalities. Despite the initial encouraging results in experiments. Further studies that are being done with innovative polymer design, with the creation of multifunctional nanocarrier systems and advancements in translational strategies, should also enhance a quicker approach to the creation of clinically useful pH-responsive nanomedicine systems to treat cancer in patients.

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