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Design and use of pH-responsive polymers in drug delivery applications

Abstract

Drug Delivery (DD) is an important matter in the pharmaceutical industry in recent decades. Scientists have found that the effectiveness of a drug can be influenced by how the drug is delivered to the body. A Targeted Drug Delivery (TDD) system enables doctors to deliver drugs to a precise part of the body (e.g. cancerous tumor). Also, it minimizes (or even eliminates) systemic side effects or damage to the tissues around the treatment site. The focus of the current study is on the most recent advancements in pH-responsive Polymer-Drug conjugates (PDC), including the activation mechanism, synthesis (generation), and description of particular features. Additionally, this research presents conjugate compounds with varied chemical structures and architectures as well as chosen samples from a variety of materials (such as books and articles). The conjugates of pH-responsive polymers and drugs are given a sneak peek. The design and development of drug pH-responsive polymers is a more intelligent platform for TDDs, according to a literature study, because of their well-established benefits, including controlled drug delivery (CDD), tumor-specific characteristics, intracellular drug delivery, and superior therapeutic effectiveness. Additionally, it removes MDR resistance and lessens both the drug's and the carrier's negative effects.

Keywords: *Drug release system, pH changes responsive, polymers sensitive to pH changes, controlled release*

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Introduction

As is well known, the capacity of polymeric nanoparticles to shield the delicate charge until it reaches the target location gives them the potential to enhance therapeutic delivery. The capacity to escape the immune system, the ability to target certain cells and tissues, and the ability to transfer charge to particular intracellular locations are only a few of the challenges to attaining successful therapeutic delivery, according to research [1]. There are currently few instances of polymer delivery systems being employed in the clinic, despite great progress being made in overcoming these barriers. Utilizing stimulus-responsive nanoparticles is one of the key methods for delivering charge to the active site. It is possible to create responsive nanoparticles such that they respond to different biological stimuli by changing their material characteristics [2]. The design of responsive nanoparticles has been influenced by a wide range of stimuli, including internal and external ones like pH or redox conditions, as well as external ones like light and temperature. Because of the pH changes that take place when nanoparticles enter a cell, pH-responsive nanoparticles are a topic of interest for researchers [3]. From 7.4 in the blood, the pH lowers to 6.5 in the early endosome and less than 5 in the lysosome. Additionally, certain extracellular areas have a pH that is lower (tumors, for example, have a pH of 6.4-6.8 and are mildly acidic). The pH-responsive materials are appealing as well. Since a wide range of polymer architectures may easily incorporate pH-responsive characteristics, pH-responsive nanoparticles can be designed [4]. Nanoparticles can be made to change their surface chemistry, shape or size, separation, or release of charge in response to pH. Regulation of cell uptake and charge release can be accomplished by using this modification in nanoparticle characteristics. In this way, pH-responsive nanoparticles offer a strong approach for creating therapeutic delivery systems [5]. The fact that endosome/lysosome membranes can be damaged by pH-responsive nanoparticles is crucial. This means that distribution to the cellular regions where therapies are most active (such as the cytosol) will always have the greatest impact. As illustrated in Fig. 1, the three primary methods for creating pH-responsive nanoparticles (for therapeutic administration) are highlighted in the current research. These methods include (a) the use of charge-delivery polymers; (ii) the use of acid-sensitive bonds to chelate iron; and (iii) the formation of cross-linked particles using acid-sensitive bonds. Recent examples demonstrate how each of these techniques may be employed to create eye-catching nanoparticle delivery systems [6]. There is rising hope that the use of nanotechnology in medicine may lead to major improvements in the identification and management of several illnesses. A variety of nanotechnology-based biomedical applications have been created as a result. They currently serve a function that is rapidly expanding in the detection and management of human illnesses [7–8]. Polymer nanoparticles, metal nanoparticles, dendrimer nanoparticles, liposomes, micelles, nanocrystals, nanotubes, and other nanostructures are just a few of the many nanoparticles (NPs) with numerous applications that have recently been made possible by developments in materials science and nanoparticle identification technology. Compared to using traditional medications, using nanoparticles provides a number of benefits. By enhancing the specificity of medication molecules through targeting, for instance, nanotherapeutics minimize drug doses. As a result, they improve bioavailability and eventually aid patient

acceptability. Reduced toxicity and greater effectiveness are the effects of using nanoparticles to deliver poorly soluble substances through easier administration routes. Multimodality is a differentiating feature of nanocarriers. Several diagnostic and therapeutic compounds can be delivered simultaneously as a result [8]. Due to their use as DDS, polymer-based nanocarriers will be the only topic of this study. DDSs with a controlled release mechanism that responds to stimulation have a lot of promise for use in therapeutic settings. Polymers are used for a variety of stimuli-responsive systems in pharmaceuticals. With a focus on the design, development, and commercialization challenges these nanomemories for drug delivery face, this research was conducted from a chemical and pharmacological point of view. Here, we will highlight future problems and clinical applications. Hence, the purpose is to design and use pH-responsive polymers in DDSs.

The pH-responsive polymers for drug delivery applications

1. DDSs

The science of nanotechnology is regarded as a potent tool for creating nanotherapies for different therapeutic and diagnostic reasons. The medicine is given and released specifically and selectively with a DDS that combines targeted delivery with controlled distribution [9–10]. Therefore, numerous aspects (such as the size, shape, and surface properties of nanocarriers) should be taken into account while choosing and building an appropriate DDS. In order to create nanotherapeutics, which is what DDSs are ultimately aiming for, it may be necessary to select a good biocompatible material with the ideal size, shape, and surface. The absorption of nanotherapeutics through mucosal routes, blood flow, the bloodstream, and elimination are all significantly influenced by size. Deeper tumor tissue penetration is achieved by small nanocarriers. Their formulation, however, is frequently challenging [11]. Nanotherapeutics less than 5 nm are removed by renal clearance, albeit they are not eliminated as quickly as molecular medicines. Mononuclear phagocytic organs frequently gather larger particles. Nanotherapeutic circulation and tissue penetration are similarly impacted by surface charges. As an illustration, cationic polymer nanoparticles circulate in the blood for a shorter period of time than anionic nanoparticles. But they can pierce deeper than anionic nanoparticles.

2. Drug release scaffold based on pH-responsive polymer

A gradient of pH between extremely acidic pH levels and physiological pH (=7.4) may be seen in the human body. The physical and chemical characteristics of polymers make them one of the most appealing DDSs. The capacity to attach pharmaceuticals at physiological pH and release them at a lower pH (lysosome pH or certain tumor settings) is only one example of how their physical and chemical characteristics enable them to adapt to very tiny changes in the environment. Smart Polymers (SP) are also excellent candidates for DDSs because of their adaptability and relative simplicity in processing and formulation. To ensure targeted delivery, increase biocompatibility, and enable high-resolution imaging, different agents can be applied to the surface depending on the kind of polymer set. Additionally, a variety of bioactive substances (including medicines, nucleic acids, and imaging contrast agents) can be encapsulated using the polymer nanocarrier. The correct scaffold must be chosen in order for DDS to produce the intended results. The right scaffolds are probably going to provide therapeutic advantages (such as improved penetration, favorable specificity, excellent pharmacokinetics, and hence advantageous medication effectiveness). Through pathological alterations, polymeric nanoparticles can efficiently enter tissues and deliver medications to certain target locations. Typically, these nanosystems deliver the medicine by encapsulating it at the target, where it is released when the microenvironment's pH changes. Polymeric NP sand is mostly made by emulsification techniques [13] employing stabilizers such as polyvinyl alcohol (PVA), in contrast to micelles and polymersomes (which self-assemble). Poly(Pactic-co-Glycolic) (PLG) nanoparticles were created by Chen et al. PDCs are possibly the most popular nanostructures for the simultaneous delivery of chemotherapeutic medications to breast cancer tumor cells (with MultiDrug Resistance, MDR), in which the drug is covalently attached to the polymer carrier through a biodegradable linker [14–15].

3. Strategy for designing DDSs based on pH-responsive polymers

Using the body's pH gradient and a few chosen pH-responsive polymers, DDSs may be created. This section discusses several methods and techniques applied in the development of pH-responsive DDSs. The processes by which pH stimuli are triggered and result in drug release are the major emphasis here [16–17]. The outcome of the delivery platform is greatly impacted by the medication pricing methodology. In general, there are two approaches to charging drugs: drug encapsulation and drug conjugation. Each approach has pros and cons. The process for making drugs is simpler and leaves the body with fewer unidentified metabolites. However, it has issues with early medication release and a lack of space for huge shipments. Contrarily, drug compounding offers a platform for delivery where high drug charges and controlled drug release are guaranteed. Additionally, compared to polymer-drug conjugates, the physical and chemical characteristics of nanocarriers are more visible because of the relatively unique structure of the nanocarrier. The polymer-

drug conjugation method has some key drawbacks, too, including the drug's requirement for a chemical functional group to assure covalency. In both situations, the medication must be stored and stabilized in the designated cases until it reaches its intended destination (i.e., the location where it is released in a regulated way as a result of pH stimulation). To achieve this, many methods were investigated in order to create the most potent pH-responsive DDS. [18]. This method has been used to develop a number of polymer-based DDSs based on protonation-deprotonation processes. They are divided into two categories: (i) Anionic and (ii) Cationic, depending on the ionizable polycarboxylic or polyamine groups. Ionizable groups often have an appropriate pH value that is near the intended target pH value and are weak acids or alkalines. The design of DDSs includes instances of pH-responsive anionic and cationic polymers [19]. One of the most commonly utilized types of polymers that react to pH is anionic. These include citraconic anhydride, polymers with sulfonamide groups, and polyacids including poly(acrylic acid), poly(methacrylic acid), poly(ethylacrylic acid), poly(glutamic acid), and poly(allylamine hydrochloride). [20]**.** These proteins become ionized and hydrophilic at physiological pH, respectively. However, they become protonated and hydrophobic in acidic environments. To enhance cancer therapy, Li et al. have created a pH-sensitive PEG-PCL-PGA-based active targeted delivery system. In the acidic milieu of the tumor cell, this polymeric nanocarrier's pH-sensitive feature causes a fast release of the medication. The breakdown of the polymer complex as a result of the change in water solubility in various pH settings (particularly neutral PGA carboxylate groups) was a key component of the drug release mechanism. [21]. The benefit of pH-sensitive cationic polymers is that they increase cellular absorption because of their positive charge surface. They are therefore promising DDSs, particularly in the treatment of cancer. The polyamines in these polymers are ionizable. At acidic pH levels, the pH value is protonated. Typically, the charge shift is what weakens the nanostructure and results in drug release. Another cationic polymer that has found widespread usage in drug delivery applications is poly(L-histidine) [22].

The pH-sensitive polymers in drug compounds: Design and Development

1. Practical mechanism of pH-responsive polymer-drug conjugates

Based on the practical mechanism, pH-responsive polymer-drug conjugates should be rationally designed. The linker of the conjugates created by the designer is often responsive to pH level fluctuations in the environment. It can undergo hydrolytic degradation, and the rate of this hydrolysis has an inverse relationship with the pH of the environment. Since many oral medications are ineffective, intravenous administration is frequently employed and is the favored technique in the field of polymer-drug conjugation. The conjugated molecules can instantly reach the circulation following intravenous delivery. It is anticipated that the drug's pH-responsive linker will maintain a stable enough state. In this way, it is ensured that the conjugates reach the diseased tissues (without any significant chemical changes during the passing medium) (pH of bloodstream = 7.4). After entering the pathological sites (e.g. interstitial tumor), macromolecular polymer-drug compounds quickly enter the cell by endocytosis. Compared to unbound drug molecules that enter the cell through the plasma membrane, this is entirely different. Phagocytosis and pinocytosis are two extremely wide subtypes of endocytosis [23–24].

2. Synthesis and description of pH-responsive features of polymer-drug conjugates

To couple doxorubicin (DOX) with a carrier polymer at first, the hydrozone bond was a component of a pH-responsive linker. Because of the reliability of the response in DDs, hydrozine has received the most attention among pH-responsive chemical bonds. The hydrazine group is an important component of hydrazine bonds. Hydrazine is simple to integrate into polymeric materials from a chemical standpoint, and the response conditions are good. In order to modify the carboxyl group of the polymer and create conjugates that include hydrazones, monoprotected hydrazines are often utilized, as illustrated in Figure 3. Chloroformate is a desirable reagent in cases where the polymer carrier has a hydroxyl group because it can operate as an active site for subsequent reactions and is sensitive to hydrazine hydrate. Drug compounds may occasionally include hydrazines. In order to create effective hydrazone conjugates, they are therefore linked to the -thiol group in different carriers of the polymer [25]. Other chemical linkages can also produce pH-responsive polymer-drug conjugates, even though the majority of research is concentrated on hydrazones. In contrast to the many different ways that hydrazones may be made, research on additional pH-responsive chemical linkages is still in its early stages, and only a small number of synthetic methods have been created. Two single-bonded oxygen atoms are joined to a central carbon in the commonly used group known as acetal. Vinyl ether, a functional polymer with a hydroxyl group, and a medication can be combined to create this molecule by acid catalysis. In vitro drug release utilizing the dialysis technique is commonly used to measure the degree of pH responsiveness in polymer-drug conjugates. In this experiment, solutions grown with various pH values—such as phosphate-buffered saline (PBS) with a pH of 7.4 (corresponding to the pH of blood) and a pH of 5.0

(corresponding to the pH of endosomes)—are used to measure the interior environment of the human body. Polymer-drug conjugates often release free medicines significantly more quickly in acidic settings than in neutral situations, depending on the pH. When drug molecules are covalently bound to polymer carriers by various linkers, diverse behaviors are shown in vitro and in vivo. For the comparative analysis of pH-responsive polymer-drug conjugates, several molecules with various acid-dependent chemical linkages were created and manufactured. While both bonds are pH-responsive, the drug release rates for hydrazone and cis-ecotonal bonds differ substantially. A hydrazone bond or a cis-acotynyl bond was effectively used by Park et al. to conjugate DOX to Poly(L-Lactic Acid)-block-Poly(Ethylene Glycol) (PLLA-b-PEG) copolymers. It was discovered that hydrazone-based linkers are a preferable alternative to the cis-acotinyl bond for pH-responsive drug delivery by comparing the drug release characteristics of these two pH-responsive bonds. Under slightly acidic circumstances, the entire intact structure of DOX may be produced from conjugates containing hydrazone. Conversely, the natural DOX was only partially released by conjugates bearing the cis-ecotinyl bond.

3. Linear polymer-drug compounds

PHPMA and PEG are the most often employed carriers for the creation of pH-responsive polymer-drug conjugates out of all the linear polymers studied and used at the bedside. Due to their innate inability to degrade, the MW of these two polymers must be kept below 40,000 g/mol in order to be eliminated from the body through the kidney. High MW in polymers, however, causes a lengthy duration in the blood, as evidenced by a wealth of research. Using the amine group of the polymer to connect the C13 carbonyl group of doxorubicin by a cis-aconityl bond, Kopecek initially reported pH-responsive PHPMA-drug conjugates. After that, other pH-responsive DDSs were created. The most prevalent type of pH-responsive polymer-drug conjugation among them is the hydrazone-based PHPMA-DOX combination. Most hydrazone-based PHPMA-DOX conjugates with significantly pH-dependent DOX release characteristics, in general, have quick and high release rates in buffers with a pH value of 5 and relatively low release rates at physiological pH. Studies conducted in vitro have shown that the toxicity of these PHPMA-drug conjugates is often on par with that of the free drug and, in some cases, even higher. The PEG copolymer (as a possible polymer carrier) is typically reformed with other polymers to create block or graft copolymers in pH-responsive DDSs. In an aqueous solution, these PEG-based copolymers are anticipated to change into a self-assembled micelle structure since they typically have highly amphiphilic properties. Almost all DDSs in cancer treatment are complicated by the establishment of multi-drug resistance (MDR). As one of the causes of MDR, extensive studies have been conducted on the increase of P-gp pump in the cell membrane. From the study point of view, nanoparticles (such as micelles) can pass through the P-gp pump system, increase the accumulation of the drug inside the incoming cell, and promote the chemical drug inside the cell. Free drugs actively cross the plasma membrane and reach the perinuclear region. Polymer-conjugated medications, however, penetrate the surrounding cytoplasm before leaving it after being liberated from conjugates in the lysosomal compartment. The distribution of drugs into cancer cells is totally altered by this procedure [26–27]. In order to create pH-responsive conjugate systems, several linear polymers besides the traditional linear polymers HPMA and PEG were utilized. Polylactide that had been functionalized with acetylene was changed into polylactide-linked aldehyde by Cheng et al. Then, using an acid-sensitive Schiff base bond, it was conjugated with DOX. The conjugate-based nanoparticles displayed acid-sensitive release behavior and up to 32% DOX charge following nanoencapsulation with a PEGylated surfactant. In the area of DOX-based conjugates, the Emrick group created a brand-new carrier known as Poly(Methacryloyl Oxide Phosphorylcholine) (PMPC). Using a pH-sensitive hydrazone link to create PMPC-DOX conjugates has benefits including (i) a prolonged plasma circulation half-life of DOX (from 15 min to 2 h), (ii) drug accumulation at the tumor site, (iii) effective tumor growth suppression, and (iv) the absence of an inherent immune response. A P-gp inhibitor and an apoptotic product called disulfiram were recently physically encapsulated by Duan et al. after being connected to a Poly(Styrene-co-Maleic Anhydride) (PSMA) carrier. The pH-sensitive drug release performance was great, and the system's synergistic impacts on tumor development were also evident. As was already indicated, both in vitro and in vivo, pH-sensitive polymer-drug conjugates are excellent choices for DDSs.

4. Dendritic polymer-drug compounds

Dendritic polymer-drug compounds are highly branched and globular molecules named called dendritic. They are used as carriers of drugs and medical materials. These compounds have (i) A low-density distribution index, (ii) Uniform molecular weight, (iii) Controllable size, and (iv) Specific chemical composition. Because dendritic cells have many adaptable end groups for drug attachment, they are desirable for pH-responsive drug delivery. Acid-sensitive drug release depends on the linker between the medication and the dendritic carrier. The application of many dendritic-drug compounds in biological systems has been constrained by their intrinsic toxicity (such as cytotoxicity, immunogenicity, and hematotoxicity), despite the fact that many of these compounds

have been found to be appealing pH-responsive DDSs. Compounds with core-shell structures can be created as a solution to this issue. A pH-responsive linker connects the medication to the dendritic core, which is active. Hydrophilic and safe polymers, mostly PEG, make up the shell. Highly branching molecules are peptide dendrites, which are composed of many little amino acid monomers. Their dendritic architecture resembles proteins and is susceptible to degradation by biological processes. Peptide dendritics persist in the circulation significantly longer than linear polymers due to their distinctive dendritic structure and high degradability. Its safety index is high [28].

5. The crosslinking polymers-drug

In cancer treatment, crosslinking amphiphilic polymers based on amphiphilic copolymers (which may form self-assembled micelles) have received a lot of attention because of their ideal size for active cancer targeting and intracellular delivery. But, the sudden release of drugs in the systemic circulation causes a serious limitation in their delivery to the patient's bedside. Recent attempts have concentrated on using cross-linking to make such cross-linked micelles more stable in order to solve this issue. Strong interactions between intraparticles can be produced through covalent crosslinking. To put it another way, the crosslinked micelles will have great colloidal stability following crosslinking. They'll be immune to both controlled medication release kinetics and destabilizing agents as a result. Additionally, the crosslinking technique can greatly enhance the performance of crosslinked micelles in vivo [29]. There are currently three widely used techniques for creating crosslinked micelles: (i) radical polymerization; (ii) a twinning agent as a crosslinker (typically cisplatin); and (iii) disulfide bridging.

6. Inorganic polymer-drug conjugates

Inorganic polymers (IP) have received a lot of interest lately for use in medicine. The majority of nanomaterials are made of inorganic polymers, which have several benefits, including (i) high body compatibility, (ii) high stability under physiological settings, (iii) simple manufacture, and (iv) simple controllability of size, shape, and surface features. More than other qualities, inorganic nanostructures' innate optical, electrical, and magnetic capabilities serve many purposes. For instance, Single-Walled Carbon Nanotubes (SWCNTs) have a very high potential to infiltrate cellular tissues and give significantly more options for drug conjugation because of their one-dimensional (1-D) structure and large surface area. The cytotoxicity and intracellular accumulation of DOX were boosted by connecting it to SWCNTs via pH-sensitive hydrazone bonding. Site-specific medication release, hyperthermia, MRI contrast enhancement, and magnetic field-assisted radionuclide treatment are just a few of the in vivo biomedical uses of body-compatible Superparamagnetic Iron Oxide Nanoparticles (SPIONs) (such as Fe3O4) [30]. Gold nanomaterials (nanorods or nanoparticles) have significant near-infrared absorption and can be used for a variety of purposes, including optical imaging and photothermal treatment. In order to create pH-responsive inorganic polymer conjugates, both of these nanomaterials have recently been joined to DOX using hydrazone bonds. These nanocomposite conjugates can enable targeted cancer treatment and PET imaging employing cRGD and NOTA, in addition to their capacity to transport and release medicines (particularly in acidic cancer tissues and cells). Mesoporous silica polymers offer rich locations for transporting many molecules with high density due to their enormous internal surface area and pore capacity. It enhances the absorption of hydrophobic medicines into the circulation and slows down the quick departure of charged molecules to the environment outside. After forming a pH-responsive hydrazone bond with DOX to form mesoporous silica nanoparticles (MSNs), these MSNs demonstrated an impressive pH-sensitive drug release mechanism. The passage of MDR through the P-gp enhancer pump was also successfully blocked. These MSNs may be made more integrable for fluorescence and MRI (using pH-sensitive drug release) by adding tiny fluorescent dye molecules and SPIONs. This opens up new possibilities for cancer detection and therapy.

Conclusions

Due to their potential to present a number of treatment difficulties (such as a poor therapeutic response and severe side effects for clinical trials), DDS targeting tumors has drawn more and more interest over the past 10 years in terms of research and development. Generally speaking, a targeted drug consists of two parts: (i) delivering the chosen drug to the target areas; and (ii) releasing a particular medication at the target site. The use of stimuli-responsive drug delivery systems based on various bodily settings might enable CDD in addition to cell-targeted biomolecules for a particular delivery. Targeted therapy research has recently been conducted in this area. A stimulus-stimulation state is a response state, and drug systems that are stimuli-responsive can produce particular responses in response to minute external changes in the physiological environment. These adjustments are triggered by both internal and external stimuli, including pH, redox potential (a chemical reaction in which the oxidation state of a layer changes), ionic strength, and lysosome enzymes. For instance, some intracellular compartments exhibit a lower pH value when compared to the matrix (intracellular substance) and typical ExtraCellular Fluid (ECF), both of which have a pH of 7.4 (such as endosomes and lysosomes with a pH of 4.5–6.5). The

pH in tumor tissues is always 0.5–0.1 units lower than in healthy tissues as a result of fast proliferation, acceleration of glucose synthesis, and storage of lactic acid. This pH differential is a significant indicator that it may be the perfect trigger for the selective release of cytotoxic drugs in tumor tissues and/or among tumor cells. Numerous high pH-responsive drug delivery methods, including liposomes, micelles (electrically charged particles/the fundamental unit of protoplasm), nanoparticles, nanogels, dendritic polynuclear nanocarriers, etc., have recently been explored. Although many devices exist and significant advances have been made, polymer-conjugated drugs are still preferred due to their clear and superior advantages. Fig. 1 shows a model of polymer-conjugated drugs commonly used in many types of research. This structure consists of (i) A hydrophilic and biocompatible polymer substructure, (ii) Hydrophobic bioactive agents (usually, confined to the polymer with a biologic responsive linker), and (iii) A target section. Drug delivery, increasing the solubility of pharmaceuticals in water, and protecting the cargo from the body's quick removal are all achieved with polymer carriers. Due to its high permeability and the Effect of preservation (EPR), the polymer's molecular weight rises, and the same pair tends to concentrate in solid tumors. Multiple medicinal molecules are covalently joined to a polymer substructure in PDC. The three key improvements of the conjugated method over conventional polymer systems (which physically encapsulate medicines in the polymer layer) are: (1) High drug capacity; (2) Enhanced drug release; and (3) High stability without the propensity for drug leakage. The therapeutic impact of each of these situations depends on them all. PDC uses an acid-sensitive bond between the medication and the polymer carrier to primarily create the pH response. Due to its high selectivity, enhanced cellular uptake, and extracellular distribution with a negligible percentage of harmed healthy cells, this stimulus-response system is particularly successful in developing a high therapeutic impact. Most importantly, this system provides a good opportunity for drug release (where a participant's delivery system is activated) to achieve the best therapeutic outcome. However, sometimes drug molecules do not have the required groups to form the appropriate chemical bond for the pH-responsive. Hence, additional chemical modification is necessary for drugs. The domain derived from these modifications is called a spacer. The speed and location of medication release, as well as their activation in many circumstances, may be managed by selecting the right chemical bond and spacer. Additionally, introducing a targeting section (like an antibody) can successfully activate medications that are site-specific.

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