ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 11| Issue: 8| August 2025|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2025: 8.691 || ISI Value: 1.188

EXPLORING RECENT ADVANCES IN pH-RESPONSIVE DRUG DELIVERY SYSTEMS

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Article DOI: https://doi.org/10.36713/epra23766
DOI No: 10.36713/epra23766

ABSTRACT

In a variety of applications, including medication delivery, tissue engineering, imaging diagnostics, and biosensors, bio responsive nano systems are becoming more and more significant. Among these, pH-responsive delivery systems have drawn a lot of interest due to their capacity to react to the microenvironment of disease and release therapeutic medications in reaction to pH. This review paper discusses four different types of pH-responsive modes, their corresponding design methodologies, applications, and future directions by cleverly designing pH-sensitive nano systems for precision imaging or therapy. This is done in light of the significance of pH-sensitive nano-delivery systems.

KEYWORD: *Bio Responsive, Delivery of drugs, Modes of response, Nanoparticles, pH-responsive.*

INTRODUCTION

Over the past few decades, nano-delivery technologies have drawn more attention in the fields of disease imaging and treatment. However, current imaging probes have some common issues with low sensitivity or insufficient specificity for the purpose of precision imaging on disease; traditional nano-delivery systems typically cannot accomplish all the goals for disease treatment, such as high drug concentration in targeting tissues or cells, long drug retention time in vivo, and fewer side effects all at once. Several stimuli-responsive and targeted nano systems that are based on variations in pH, temperature, ATP, redox levels, and reactive oxygen species levels in the healthy and pathological states have been used extensively to get around these difficulties. These bio responsive nanomaterials outperform other materials in terms of selectivity, drug distribution in vivo, toxicity, and imaging efficiency than conventional carriers.

pH is a vital physiological signal that is essential for preserving tissue and cell homeostasis. Mesenchyme in tissues has a pH that is precisely balanced between 7.2 and 7.4. Membrane transport, receptor cycling, lysosomal degradation, and viral entrance into cells are all directly impacted by the pH of intracellular compartments (such as endocytic vesicles) in eukaryotic cells. [1], [2], [3]. At the molecular level, ATP generation depends on the pH gradient on the mitochondrial membrane [4]. Apart from its typical physiological impacts, pH plays a role in a number of pathological processes, including as infection, inflammation, and cancer. As a result, pH-responsive nano-delivery devices that use pH as a stimulation signal are crucial for both treating associated diseases and imaging them [5].

The physiological/pathological pH signal, pH-responsive nanomaterial response mechanisms, fabrication techniques, and applications will all be covered in this review.

1. THE PH SIGNAL UNDER PATHOLOGICAL AND HEALTHY CONDITIONS

1.1. Signals of physiological pH

The pH value fluctuates at different locations and stays relatively stable under typical physiological settings (Table 1), which is essential for preserving the body's physiological processes.

Site	pH value
Plasma	7.38–7.42
Saliva	6.0-7.0
Gastric juice	1.0-3.5
Bile	7.8
Pancreatic fluid	8.0-8.3
Small intestinal fluid	7.5-8.0
Coliform fluid	5.5-7.0
Lysosomes	4.5-5.0
Golgi apparatus	6.0-6.7

pH values in physiological conditions are shown in Table 1.

1.2. Signals of pathological pH

Compared to normal tissue, diseased tissues have a substantially altered pH. For example, primary tumors, metastatic tumors, and inflammatory areas have lower pH values. According to reports, 60 hours after inflammation develops, the local pH of inflammatory tissue drops from 7.4 to 6.5 [6]. Because tumor cells actively glycolyze in oxygen-rich environments, they display a "reversed" pH gradient in the setting of the tumor microenvironment, with normal or slightly higher cytoplasmic pH and lower extracellular pH (pHe = 6.8) [7]. The "Warburg" effect is the name given to this metabolic feature of aerobic glycolysis, which is characterized by increased uptake of glucose, active glycolysis, and a high concentration of lactic acid metabolite. As a result, the pH outside the cell (pHe) and inside the intracellular acidic vesicles (pHi) is noticeably lower than in normal cells. One frequent characteristic of cancer has been thought to be a pH imbalance [8].

2. HOW PH-RESPONSIVE NANOPARTICLES REACT

In order to accomplish targeted medication release in organs and tissues, oral delivery systems can be designed to take advantage of the pH gradient in the gastrointestinal tract. Stimulus-responsive delivery systems typically employ the local acidic environment of a tumor or inflammation to regulate medication release [9]. For acid-sensitive nano-delivery devices, endosome acidification provides the optimal pH gradient at the cell and organelle level [10], [11].

Typically, non-responsive amphiphilic block copolymers self-assemble into micelles, with the hydrophobic cores encasing or conjugating medicinal molecules or fluorescent dyes. The micelles are kept stable by the hydrophilic blocks of the polymeric micelles extending outward to form a stable shell [12]. pH-responsive nano systems, as opposed to traditional polymeric micelles, experience physical or chemical changes in acidic environments, including swelling, dissociation, and degradation. This allows the loaded drug or fluorescent dyes to be released efficiently, enabling precision imaging or spatiotemporal control of therapy [13], [14], [15].

1)Physical dissociation, 2) chemical bond cleavage-induced nanoparticle dissociation, 3) chemical bond cleavage-promoting payload release, and 4) nanoparticle swelling are the four categories of response modalities of common pH-responsive nano systems. The primary cause of pH responsiveness in polymeric materials is the protonation of ionizable groups or the acid hydrolysis of chemical bonds; conformational or chemical alterations can also produce this effect [16]. Conformational change is frequently the consequence of molecular self-assembly brought on by an outside stimulus. The hallmark of the supramolecular self-assembly system proposed by Whitesides is positive synergy, which typically results in very high response sensitivity when compared to small molecule sensors. Molecularly, ionic connections in the nano-core, hydrogen bonds, π-π stacking, or hydrophobic interactions may all contribute to the responsiveness of pH-sensitive nano systems [17].

2.1 Dissociation in the body

The term "physical dissociation mode" describes how nanoparticles react to a particular pH environment, which causes hydrophobic core protonation or ionization and ultimately physically dissociates the nanoparticles (Fig. 1a).

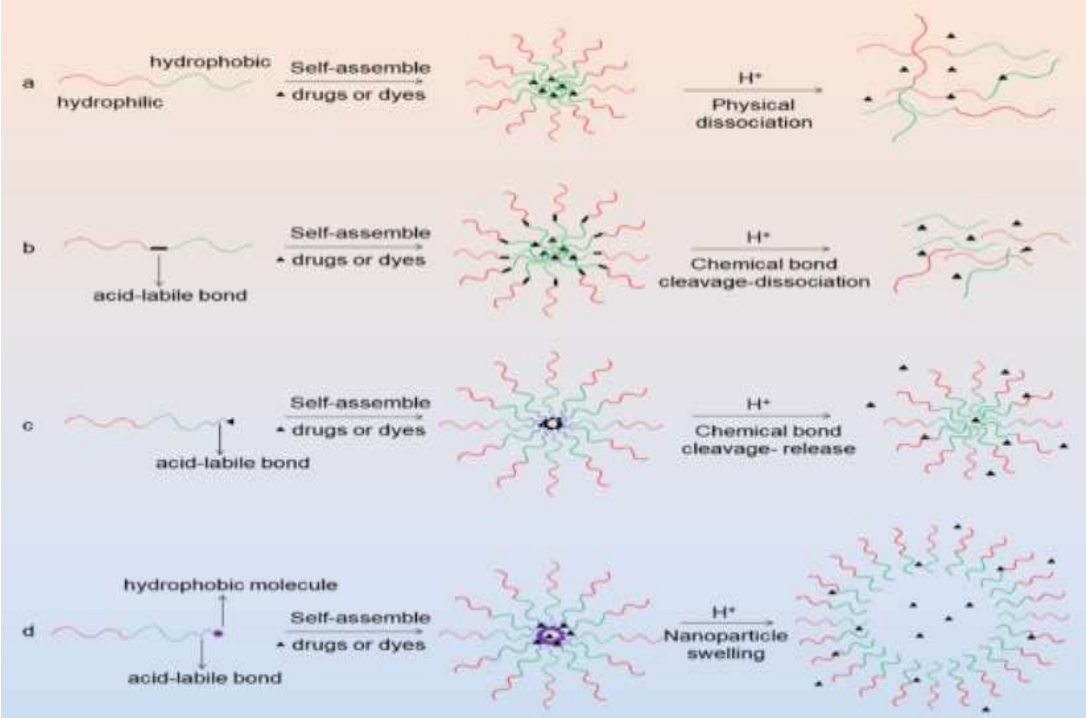

Figure 1: Acid-sensitive pH-responsive polymeric micelle release mechanism (a) physical dissociation; (b) dissociation of nanoparticles due to chemical bond cleavage; (c) release of payloads facilitated by chemical bond cleavage; and (d) swelling of nanoparticles [18], [19].

By conjugating fluorescent dyes or medications to block copolymers, physical dissociation can be used to create ON/OFF fluorescence probes or drug repositories. Because of the homomeric fluorescence resonance energy transfer (HomoFRET) effect, hydrophobic fluorescent dyes conjugated or encapsulated in the core of nanoparticles remain silent ("OFF" declared) in aqueous solution. A hydrophobic segment with a polymeric ionizable group (like a tertiary amine) is protonated or ionized in an acidic environment. When the hydrophobic segment reaches a hydrophobic threshold, the charged polymer is cooperatively de-protonated by the nanophase separation [20], which decreases its hydrophobicity and breaks down the polymeric micelles, turning the nanoparticles into fluorescent monomers and putting the system in the "ON" state.

Polymers containing ionizable groups that act as proton acceptors or donors in reaction to pH variations in the environment make up the physically dissociation nanoparticles that are sensitive to acidic environments. Groups like acrylic acid, sulphonamide, and tertiary amine may experience protonate or charge reversal in an acidic environment, which will increase their water solubility or mutual repulsion. This will dissolve the polymer and release the medication or color [21], [22], [23]. In order to create micelles through copolymerization, groups containing nitrogen typically function as hydrophobic segments of nanoparticles and polyethylene glycol (PEG) as hydrophilic segments. The nanoparticles dissolve as a result of electrostatic repulsion created when the nitrogen on the hydrophobic region protonates.

2.2. Dissociation of nanoparticles due to chemical bond cleavage

The dissociation mode of chemical bond cleavage-resulting nanoparticles is the mode in which the hydrophobic and hydrophilic fragments' chemical bonds break and cause the nanoparticles to dissolve (Fig. 1b).

Drug/fluorescent dyes are contained by self-assembling nano-micelles, and hydrophilic and hydrophobic segments of amphiphilic block copolymers are joined by acid-labile chemical bonds in the chemical bond cleavage-resulting nanoparticle dissociation system. The micelles stay stable and the encapsulant won't be released at physiological pH levels. The acid-labile link breaks when H+ reaches the micelles in an acidic environment, causing the polymer to dissolve and release medication or fluorescent colors.

For this type of delivery mechanism to release the payload efficiently, a specific pH level is needed. In a prior investigation, doxorubicin was loaded using a copolymer of dextran and retinaldehyde connected with hydrazone. Less than 10% of retinaldehyde breaks off after 24 hours at pH 7.4; the percentage of broken bonds rises significantly at pH 6.5; and it exceeds 70% at pH 5.0. This suggests that a specific pH value is necessary for the method to release the medication effectively through enough bond breaking [24].

2.3. Payload release through chemical bond cleavage

The cleavage of acid-labile bonds that link the drug/dye and the hydrophobic portion of the nanomaterial (Fig. 1c) is what causes drug/dye release in the chemical bond cleavage-promoting payload release paradigm [25] [26]. This technique creates polymeric micelles by conjugating drug/fluorescent dyes onto hydrophobic regions of block copolymers using chemical bonds that are labile to acid. The polymer is typically stable and does not leak any drugs or fluorescent agents while the micelles are in normal physiological circumstances. However, the drug/fluorescent dyes will be released when the polymer reaches acidic places (like tumors) since the acid-sensitive chemical linkages will be hydrolysed. There are numerous typical acid-labile bond options, and since the pH values of these bonds vary depending on the acid sensitivity, the best option should be selected.

The fracture of the chemical bond Polymers containing chemical linkages that are labile to acid are used to create pH-responsive nano systems. There are typically two methods for building the systems, depending on the conjugation site. One is to physically encapsulate medication or fluorescent dye molecules into nano systems by joining PEG and hydrophobic segments with acid-labile bonds. The structure of the nanoparticles is destroyed and the medication or luminous dye is released when the acid-labile links cleave in an acidic environment. The alternative tactic is to use an acid-labile structure, which reacts to acidic conditions, to conjugate a medication or fluorescent dye to a hydrophobic section of the polymer. An efficient method for releasing payloads via acid-labile bonds in an acidic environment is the hydrolysis of acid-labile bonds that exist between drugs or fluorescent dyes and polymers or within polymers.

Hydrazone, imide, ester, ortho ester, acetal, and other acid-sensitive structures are frequently employed [27], [28], [29], [30]. The payload is released when the bond breaks due to the action of H+. Fig. 2 illustrates the structure of acid-labile bonds.

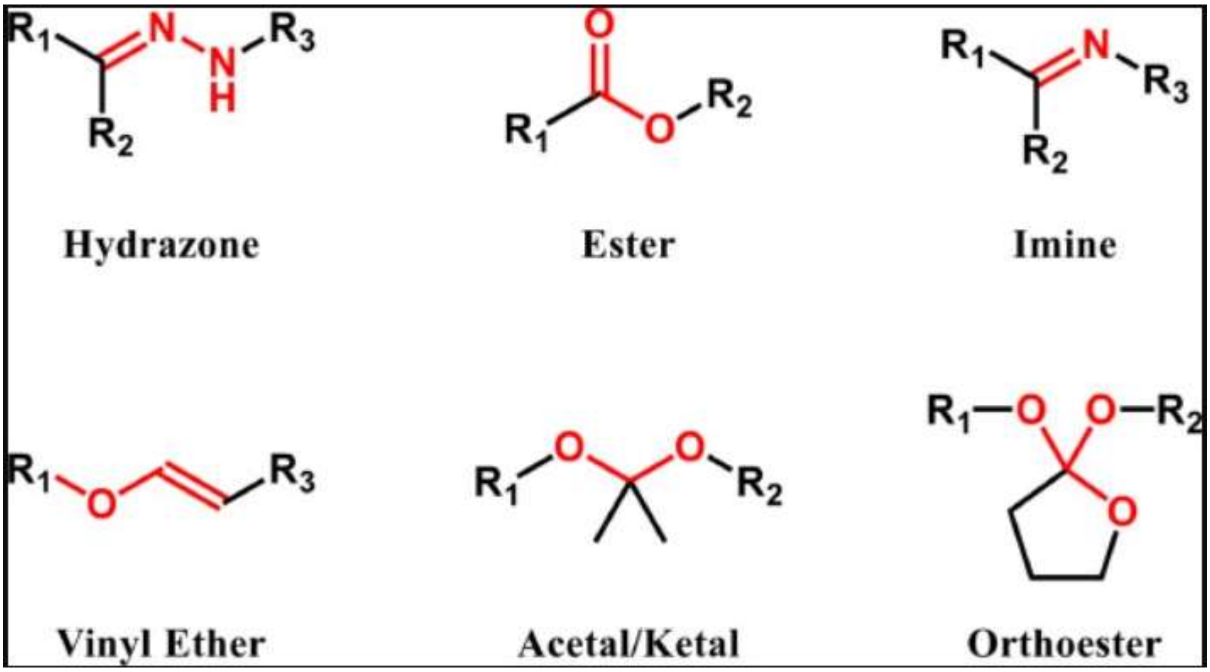

Figure 2: Acid-labile chemical linkages used in pH-sensitive nano systems and their structure.

2.4. Swelling of nanoparticles

The mode known as "swelling mode" is when pH-sensitive nanoparticle micelles expand to begin payload release (Fig. 1d) [19] [25].

Based on the swelling polymeric micelle design principle, long hydrophobic chains were joined to hydrophobic segments in the proper proportion by acid-labile chemical bonds. The hydrophilic-hydrophobic block ratio was regulated to allow nano micelles to self-assemble in aqueous solution at physiological pH levels. H+ enters the polymeric micelles when they reach an acidic environment, like tumor tissues, and encourages the breakdown of the acid-labile chemical bonds, breaking off hydrophobic fragments and increasing solubility. This causes the micelles' volume to increase, which in turn causes payload leakage or release from the core pores.

In this manner, certain hydrophobic segments are joined to the chain via acid-labile bonds, and the hydrophilic and hydrophobic segments copolymerize in the appropriate ratio. When the connection breaks in an acidic environment, the hydrophobic portion of the amphiphilic segments' polymerization level drops, which is followed by a decrease in the micelles' overall hydrophobicity. This increases the volume of the polymeric micelles and their porosity, allowing the payload to be released. The most popular technique in this approach is to use an acetal bond to join 2,4,6-trimethoxybenzaldehyde with a hydrophobic segment. Because acetal hydrolysis reduces the hydrophobicity of hydrophobic segments, it causes micelle expansion under acidic circumstances [31].

3. APPLICATION OF PH-SENSITIVE NANO SYSTEMS

Fluorescent dyes, small molecule medications, antigens, and other substances can be conjugated or encapsulated using pH-responsive nano-delivery systems to facilitate immunotherapy, medication treatment, and disease site imaging.

3.1. Chemotherapy and tumor imaging

Because tumor cells have a greater metabolic rate than healthy tissues, too many acidic metabolic byproducts build up in the extracellular matrix of the tumor, causing the pH of the tumor microenvironment to drop locally. Acid-labile pH-responsive polymeric nano micelles can be used to improve therapeutic action efficiency and minimize side effects by controlling drug release in tumor tissues rather than normal tissues or throughout the delivery process in an acidic environment.

Molecular imaging enhances the intervention through image-guided drug distribution or surgery by using target-specific probes to visualize and quantify biological molecules in vivo without causing any harm. These include [32], [33], [34], [35], [36], [37], [38], [39], [40]. As a result, one of the keys uses for pH-sensitive fluorescent probes is now tumor cell imaging. The fields of analytical chemistry, bioanalytical chemistry, cell biology, pharmaceuticals, and tumor tissue imaging have all made extensive use of pH-sensitive fluorescence probes. In healthy physiological tissue, pH-responsive fluorescence probes are in the "OFF" state and not activated. On the other hand, the fluorescence probe is particularly triggered and changes into the "ON" state in an acidic tumor environment. The ON/OFF fluorescent probe's strong signal-to-noise ratio allows it to image the tumor boundaries precisely with minimal background interference, making it ideal for imaging-guided surgery. Zhao et al. developed acid-sensitive PEG-b-P (EPA100-r-ICG3) probes for tumor imaging; hydrophobic micelles and fluorescence resonance energy transfer (homoFRET) cause the fluorescence to be muted when pH rises over 6.9 [41]. If not, the fluorescence is triggered when the polymeric micelles split into monomers. By differentiating between tumor tissues (pH 6.84) and normal tissues (pH 7.4), the nano-fluorescent probe with a pH 6.9 transition point significantly increases the precision of tumor margin identification [42].

pH-sensitive nanomaterials can enhance the delivery of chemotherapy medications to malignant tumors, increasing the effectiveness of treatment. Based on the biological properties of pH and redox balance, Zhou et al. created a stable micelle-structured, non-selective drug delivery nanoparticle. Hydrogen bonds in DOX, CMCC, and CTS make up DOX@CTCP. A single crosslinked nanogel can be created by conjugating chitosan with sodium tripolyphosphate when carboxymethyl chitosan (CMCC) is present. Due to its high drug loading capacity, chitosan (CTS) was chosen as a matrix loaded cationic anticancer drug doxorubicin (DOX) for loading biodegradable nanogels. In animal tests, DOX@CTCP therapy demonstrated the greatest suppression of tumor growth in male C57BL/6 J mice with H22 hepatocellular carcinoma, and the mice lived longer. The bioavailability and therapeutic efficacy of pH-sensitive nanomedicine are higher than those of conventional nanomedicine. To accomplish tailored drug accumulation, future research must still enhance the toxicity and in vivo compatibility of cross-linking agents or monomers and create a gel with greater sensitivity [43].

3.2. Delivery in the gastrointestinal tract

One of the most popular routes of administration is the gastrointestinal tract, which offers the benefits of high safety, convenient use, and adjustable dosage. Poor solubility, low bioavailability, partial absorption, first-pass action, hazardous side effects, etc. are some of the drawbacks of certain medications.

An oral drug delivery system must be able to react to variations in the pH of the gastrointestinal tract in addition to tolerating the enzymes present in the gastrointestinal tract. The optimal oral drug delivery method should distribute the medication constantly over a predetermined amount of time without experiencing bursts. When oral drugs are made with pH-responsive materials, the delivery system's structural integrity is maintained, preventing the medication from leaking into the gastric juice (pH 1.0–2.5) and allowing the payload to enter the intestinal tract (pH 5.1–7.8) in a comparatively short amount of time (8–10 hours). In addition to preventing drug deposition on intestinal epithelium and consequent burst release, this mode of action also lessens drug leakage in gastric juice (maintaining the aggregation state at low pH).

A pH-sensitive oral drug delivery system based on CMC/HNT-AT nanohydrogel was developed by Hossieni-Aghdam, S.J. et al. [44]. The polymer's swelling efficiency and the release of the payload atenolol are both noticeably higher at pH 6.8 than they are at pH 1.2 and 4.5. It demonstrates how well the CMC/HNT-AT beads release in mildly acidic environments, suggesting that they could be employed as a novel oral drug carrier for regulated and prolonged drug release.

3.3. Immunotherapy

As we know, immunotherapy refers to the treatment method of artificially increasing or inhibiting the immune function of the body with the aim to treat diseases. Numerous immunotherapy techniques exist that can be used to treat a wide range of illnesses. Anti-tumor immunity and anti-infective immunity, for instance, are intended to stimulate the autoimmune system, which depends on its capacity to eradicate infections or tumor cells. Individual immunity must be suppressed in order to lessen the harm caused by some autoimmune disorders and inflammatory reactions.

The use of pH-sensitive materials can significantly enhance the targeting of different immunotherapy medications, increase the therapeutic benefit while lower the toxicity and adverse effects of medications. For instance, inflammatory bowel disease (IBD) can be effectively treated by using pH-sensitive nanoparticles to carry drugs to the colon. In order to treat IBD, Meissner, Y., et al. administered tacrolimus to the colon using pH-sensitive Eudragit, which had a far higher bioavailability and therapeutic impact than oral formulations [45]. In addition to preventing premature drug absorption until the medication is absorbed in the distal end of the ileum, drug delivery via pH-sensitive nanoparticles can lessen adverse effects including nephrotoxicity.

Moreover, by delivering antigens or immunoactivities for immunotherapy, pH-sensitive nanoparticles can also stimulate humoral or cellular immunity; this type of nano-delivery system is known as "nano vaccine". In order to improve the therapeutic effects of tuberculosis while lowering systemic distribution and harmful side effects, Nuhn, L. et al. covalently bound imidazoquinolinone molecules to pH-sensitive polymeric materials, which were then delivered to lymph nodes and caused antibody secretion [46].

To boost immunity, Min Luo and others have developed pH-sensitive polyacrylamide-based materials in recent years. They created a strong cytotoxic T-cell response by combining and assembling the antigen with pH-sensitive nanoparticles [47]. This pathway, which depends on interferon gene stimulators, successfully stopped the growth of cancerous tumors like colon cancer and melanoma. These include the polymer PC7A, which effectively activates cGAS-STING (cGAMP synthase-stimulator of interferon genes), a target for tumor therapy. Later, Suxin Li and others demonstrated that PC7A activated STING in a different way than cGAMP, which is a natural substrate for STING. In vitro and in vivo, PC7A activated STING more slowly than cGAMP, but it did so for a longer period of time. In the meanwhile, it might have a safer and more potent anti-tumor impact and overcome the systemic toxicity brought on by cGAMP [48].

The safety and improved degradation of ultra-pH sensitive (dUPS) polymers were created by Xu Wang and colleagues based on the aforementioned research. Similar to PC7A, one dUPS polymer, PSC7A, can activate STING, resulting in anti-tumor immunity. The therapeutic window for this pH-sensitive material is greatly expanded by the dUPS system, which offers better safety, a shorter duration of injection-induced acute inflammatory reactions, and faster healing than the UPS system. This opens up more opportunities for the clinical use of polymer materials [49].

4. CONCLUSIONS

pH-responsive nanoparticles have drawn more attention in the last ten years due to their potential uses in medication administration, disease imaging, and nanobiotechnology [50].

As a result, an increasing number of natural or eco-friendly polymers have been created [51] [52]. Additionally, pH-sensitive materials have steadily found use in a wider range of sectors, including more sophisticated immunotherapy, photothermal therapy, and classical drug delivery [53]. Although there are several published studies on pH-sensitive nanoparticles, few of these technologies have made it to the market or clinical trials due to issues with safety, clinical efficacy, or industrial scaling-up [54].

Although some pH-sensitive nanoparticles show good response efficacy or performance *in vitro*, they may be restricted by the complex physiological or pathological environment in vivo52. Firstly, the response action of some pH-sensitive nanoparticle may be restricted by the low levels of stimuli factors *in vivo*. Secondly, the cleavage of some pH-sensitive chemical bonds requires extended period, limiting the response speed of the corresponding nanoparticles *in vivo* [55]. Finally, the effective release of payloads from nanoparticles is another concern for pH-sensitive nano systems [56].

In view of the complexity *in vivo*, various pH-responsive modes and system development strategies should be selected in the early design for different purposes of application. From the perspective of material design, an ultra-sensitive and specific transition pH should be needed by subtle polymer design to distinguish the slight differences between disease tissue and normal tissue [50]. In some cases, the development of a fine-tune library of nanoparticles with different transition pH is also necessary to find the optimal polymers and cope with the inhomogeneity of acidity *in vivo* [57]. Finally, time sensitivity of pH response is equally important in nano system development. Considered mild acidic environment and dynamic distribution of nanoparticles *in vivo*, fast response speed is indispensable for specific drug release or molecular imaging at tumour site. Considered mild acidic environment and dynamic distribution of nanoparticles *in vivo*, fast response speed is indispensable for specific drug release or molecular imaging at tumour site.

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