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# MAGNETIC AND pH SENSITIVE NANOPARTICLES FOR CANCER DRUG DELIVERY

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## ABSTRACT

Cancer remains a leading cause of death worldwide with more than 10 million new cases every year. Tumor-targeted nanomedicines have shown substantial improvements of the therapeutic index of anticancer agents, addressing the deficiencies of conventional chemotherapy, and have had a tremendous growth over past several decades. Due to the pathophysiological characteristics that almost all tumor tissues have lower pH in comparison to normal healthy tissues, among various tumor-targeted nanomaterials, pH-responsive polymeric materials have been one of the most prevalent approaches for cancer diagnosis and treatment. In this review, we summarized the types of pH-responsive polymers, describing their chemical structures and pH-response mechanisms; we illustrated the structure-property relationships of pH-responsive polymers and introduced the approaches to regulating their pH-responsive behaviors; we also highlighted the most representative applications of pH-responsive polymers in cancer imaging and therapy. Many strategies based on stimuli-responsive nanocarriers have been developed to control the drug release and avoid premature release. Here, we focus on the use of the subtle changes of pH between healthy and diseased areas along the body to trigger the release of the cargo. The application of nanotechnology to medicine constitutes a major field of research nowadays. In particular, the use of mesoporous silica and carbon nanoparticles has attracted the attention of numerous researchers due to their unique properties, especially when applied to cancer treatment.

**Keywords:** pH responsive polymers; nanomedicine; Mesoporous nanoparticles, tumor imaging; drug delivery

# INTRODUCTION

The application of nanotechnology in health and medicine, so-called nanomedicine, is one of the most promising and exciting research areas nowadays.

The design of nanoparticles to address disease and to monitor and protect human health is expected to revolutionize the medical field in the next few decades. In this sense, the capacity of producing nanoparticles in the range of 20–200 nm in diameter has fueled the design of

materials large enough to escape clearance through the kidney and small enough to present long circulation times into the bloodstream. Although nanoparticles have been applied against lung, kidney, rheumatoid arthritis, diabetes or neurodegenerative diseases[1-5], among others, the first steps of nanomedicine research have been mainly focused on the challenging area of cancer, either on diagnosis or treatment. Current cancer treatments concern the use of radiotherapy, surgery or chemotherapy. Unfortunately, chemotherapeutics are administered systemically and do not show selectivity for cancer cells. Because of that, chemotherapy is considered to be aggressive for patients, since the drugs distribute all along the body instead of only near the damaged area. Then, it would be desirable to target the chemotherapeutics only to cancer cells. Nanotechnology is a rapidly expanding field, encompassing the development of man-made materials in the 5–200 nanometer size range. This dimension vastly exceeds that of standard organic molecules, but its lower range approaches that of many proteins and biological macromolecules. In the scientific world, the term "nano" is, however, somewhat ambiguous since it does not designate the same reality for physicists, chemists and biologists. Conceptually, nanotechnologies in general and nanoparticles in particular have revolutionized the administration of medicines. An ideal nanoparticle for drug delivery should be able to entrap the maximum amount possible of pharmaceutical agents. To avoid that, the surface of the nanoparticles can be decorated with hydrophilic layers to prevent opsonization (and therefore, the action of macrophages) [6–8]. The nanoparticles can accumulate in the tumor via passive targeting due to the abnormal vasculature of solid tumors (the so-called Enhanced Permeability and Retention effect)[9] and then selectively internalize the cancer cells via active targeting

### Types of Nanoparticles:

### Non-Porous

In the last few years, a number of non-porous nanoparticles for biomedical applications have been developed. It is possible to find both organic and inorganic platforms, such as liposomes, polymeric nanoparticles, dendrimers, magnetic nanoparticles or metal nanoparticles, among others[11]. In fact, there are some examples of those non-porous platforms commercially available, such as: (1) paramagnetic iron oxide nanoparticles (e.g., Venofer, Resovist); (2) liposomes (e.g., Doxil, Caelyx); (3) biodegradable polymer nanoparticles (e.g., Somavert, Cimzia); or even (4) drug-antibodies conjugates, in which those antibodies guide the drug towards the targeted cells (e.g., Mylotarg)[12].

### Mesoporous Nanoparticles

Mesoporous nanoparticles have recently attracted the attention of nanomedicine researchers thanks to their robustness, their high loading capacity and the easy chemical functionalization of their surface. This offers a great potential for targeted drug delivery and controlled release of chemotherapeutic drugs. Mesoporous Silica Nanoparticles. The synthesis of mesoporous silica nanoparticles (MSNs) is based on the sol-gel process, in which successive hydrolysis and condensation steps of the silica precursors lead to the formation of a network of silica. That polymerization process is carried out in the presence of surfactants as structure-directing agents (Figure1a). The final meso structure would depend on the type and concentration of surfactants and also on certain experimental parameters, such as temperature. Then, removing the surfactant would lead to mesoporous materials with empty mesopores, where drug molecules would be loaded. A modification of the Stöber method is employed to obtain nanoparticles with mesoporous structures, which is based on using very dilute conditions during the sol-gel process. In a typical synthesis, cetyl trimethyl ammonium bromide (surfactant) is dissolved in pure water in the presence of sodium hydroxide so that the surfactant organizes in cylindrical micelles. After that, tetraethyl orthosilicate (silica precursor) is added dropwise, and the silica network is formed through the hydrolysis and condensation of the silica precursor around the micelles. Finally, the surfactant is removed from the mesopores through extraction with either a methanol/HCl or ethanol/ammonium nitrate solution, giving rise to nanoparticles with a hexagonal distribution of empty pores (Figure 1b).
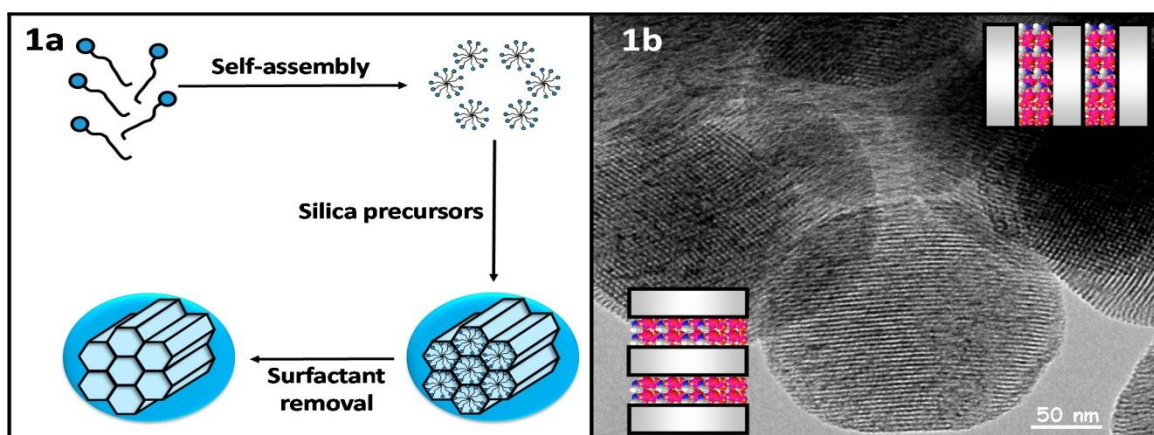


**Figure 1:** (a) Scheme synthesis of mesoporous silica nanoparticles through a modified Stöber (b) Transmission Electron Microscopy micrography of the pore distribution of MCM-41-type mesoporous silica nanoparticles.

## Mesoporous Carbon Nanoparticles

In the last few years, mesoporous carbon nanoparticles have received increasing attention by nanomedicine researchers since mesoporous carbon nanoparticles (MCNs) show similar structural properties as MSNs. Moreover, MCNs show enhanced laser absorption in the near-infrared (NIR) region that leads to an efficient conversion of light into heat that can be applied to antitumor therapy[13]. The synthesis of MCNs can be accomplished by either hard or soft templating approaches[14]. The hard templating approach is based on the use of presynthesized organic or inorganic templates. The template serves as a mold for the replication of the mesoporous carbon materials, and no significant interactions between the carbon precursors and the template are observed. A typical synthesis involves four steps: (1) preparation of the porous silica template; (2) impregnation of the silica template with the precursors; (3) cross-linking and carbonization of the organic precursors (e.g., phenolic resins, sucrose); and (4) dissolution of the silica template. On the other hand, the soft templating approach is based on the generation of nanostructures through the self-assembly of organic molecules, such as surfactants.

## Stimuli-Responsive Nanoparticles

As has been mentioned before, nanoparticles are attractive in drug delivery applications due to their ability to host drugs within them. An efficient drug delivery system would travel along the body without releasing the cargo until reaching the diseased area, where the drugs would be released. To achieve that, the concept of stimuli-responsive drug delivery arises. It is based on the use of stimuli to trigger the release of the payload only under specific conditions, i.e., those of the damaged area. This concept is particularly useful when using mesoporous silica or carbon-based nanoparticles because they present an open structure. Then, the drugs can be loaded through diffusion within them, but the cargo can also diffuse out when placed in aqueous media. This clashes with the desired release of the drugs only in the target area. Although the electrostatic interactions between nanocarriers and guest molecules may help to retain the cargo, as will be seen in the following section, an extended strategy is the use of molecular structures capable of blocking the mesopores. These structures are referred to as gatekeepers, which are organic or inorganic structures capable of hampering the release at physiological conditions and suffering some kind of structural change when a certain stimulus is applied, which would open the pores and trigger the drug release. The gates can be opened through external or internal stimuli (Figure 2).
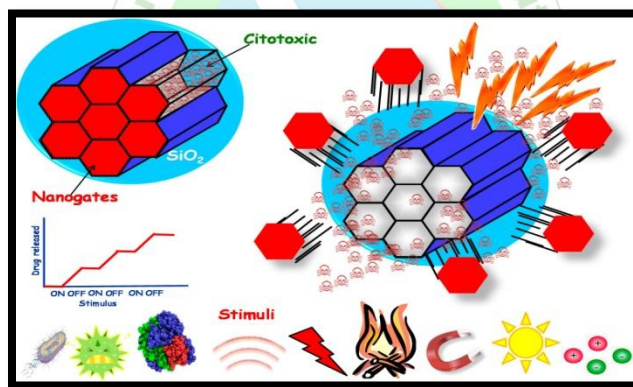


**Figure 2:** Stimuli-responsive nanoparticles where the drug release can be triggered through the application of many different stimuli.

## External Stimuli-Responsive Nanocarriers

External stimuli-responsive nanocarriers are those in which the opening of the pores is mediated by some stimulus coming from the outside of the body. The main advantage of this kind of system is that the stimulus can be modulated, opening and closing the gates on-demand in many cases, as they are applied through external equipment. The literature provides examples of temperature[15-16], magnetic[17-18], light[19–21] or ultrasound-sensitive[22] systems. The use of magnetic and thermo-responsive nanoparticles has also been reported, as they are synergic stimuli because heat can be generated by applying an alternating magnetic field[23-24].

## Internal Stimuli-Responsive Nanocarriers

Internal stimuli-responsive nanocarriers are those in which the behavior of the gate is modulated by some stimulus from the inside of the body. It is well-known that during some diseases, the determined enzymes may be overexpressed[25] or the concentration of reducing agents may increase inside the cell with respect to the outside[26]. These abnormal situations lead to enzyme-[27-28] and redox-responsive[29-30] drug delivery systems, among others. Interestingly, as will be discussed during the following sections, the value of the pH is not kept constant along the body. Then, these subtle changes in pH can be taken advantage of to design pH-responsive drug delivery systems that only release the payload when the pH deviates from the physiological value.

## The Role of pH in Drug Delivery

The maintenance of the different physiological pHs along the body is of vital importance for the organism to keep alive. For instance, variations in pH of body fluids within 7.35 and 7.45 can be corrected, but greater alterations may lead to acidosis or alkalosis events that may even cause

death. However, that rule does not always apply, and these variations can be taken advantage of in different scenarios throughout the body to design pH-responsive nanocarriers.
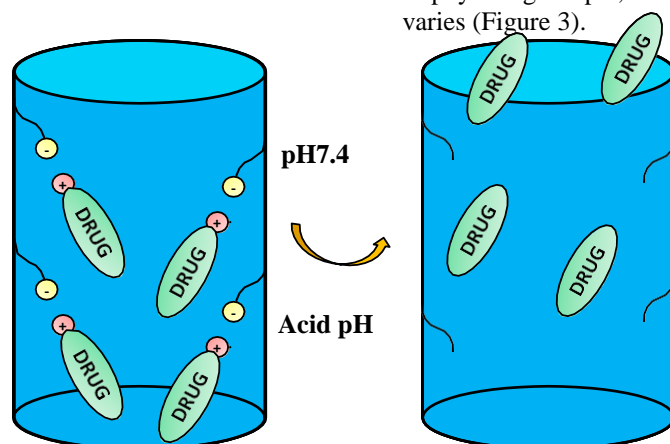
## Host-Guest Interactions



**Figure 3**: Example of host-guest interaction-based drug delivery involving cationic drugs.

Depending on the ionic nature of the therapeutic agents, a specific nanocarrier functionalization should be chosen. Generally speaking, positively-charged nanocarriers should be used when using an anionic drug in order to maximize the loading capacity and achieve a controlled released and vice versa [32-34]. One of the most used drugs against cancer is doxorubicin (DOX). DOX is a cationic drug that has been widely used for more than 30 years to treat different types of tumors. It has shown great treatment potential, but its lack of cancer cell selectivity makes it a double-edged sword because it kills not only malignant, but also healthy cells. The action mechanism is complex, but, briefly, it enters the cell through diffusion due to its high affinity to bind to the proteasome of the cytoplasm. Once there, it interferes with the topoisomerase II-DNA complex, leading to the formation of double-stranded breaks of the DNA, causing cell death [35]. Although the literature on mesoporous nanoparticles mostly provides DOX-based papers, the study of the host-guest interactions with some other drugs, such as ibuprofen, 5-fluoracil, mitoxantrone, methotrexate or sulfasalazine, has also been reported [31].

## 2.pH-Responsive Polymers Fabricating

pH responsive polymeric nanomaterials has been rapidly developed after the emerging of advanced techniques in polymer synthesis, especially reversible-deactivation radical polymerization such as ATRP and RAFT [36-37] The technical state of the art allows for precise control over molecular weights and molecular weight distributions, affording polymers with well-defined topology structure [38-40].

The pH responsive polymers can be mainly classified into two categories:

**Polymers with ionisable moieties**

**Polymers that contain acid-labile linkages**

## pH Responsive Polymers with Ionizable Groups

The pH response arises from the reversible protonation and deprotonation of ionizable groups at the molecular level.

An extended strategy to provide the nanocarriers with pH sensitivity is through the electrostatic interaction between the functional groups from the carrier and those of the drugs at physiological pH, as well as the lack of them when pH varies (Figure 3).

The pKa of a polyelectrolyte, which is defined as the pH with equal concentration of the protonated and deprotonated forms, can serve as a critical benchmark to reflect the polymer ionization behaviors at various pH levels [41]. In general, there are two types of ionizable polymers: basic polymers that accept protons at a relatively low pH and acidic polymers that release protons at a relatively high pH. Consequently, these polybases or polyacids can form positively or negatively charged polymer chains at different pH levels. Common basic moieties include amines, pyridines, morpholines, piperazines; and common acidic groups include carboxylic acids, sulfonic acids, phosphoric acids, boronic acids, etc. [30]. Among them, amines, especially tertiary amines, have drawn particular attention due to their ease to prepare and the feasibility to finely tune their pKa [42-43]. It was reported that the amines can present a marginally lower pKa when substituted with longer hydrophobic chains [44]. Recently, designed a series of ultra-pH sensitive (UPS) polymers for real-time tumor imaging [45–48]. These nanoprobes can sharply respond to and amplify in vivo pH signals in a very narrow pH span. The UPS nanoparticles are comprised of an amphiphilic block copolymer: PEG-b-PMA, where PEG stands for hydrophilic poly (ethylene glycol) and PMA is a hydrophobic segment based on poly methacrylates with tertiary amine substituent. At physiological pH (7.4), the block copolymers stay as core-shell micelles driven by self-assembly. Acid-triggered dissociation of micelles enable the increase of fluorescence intensity for molecular imaging and release of cargo for drug delivery. Yan et al. further expand the UPS polymer design based on biodegradable polypeptides (Figure 4) 49. They modified the peptides with ionizable tertiary amines for pH responsive behavior. Hydrophilic and hydrophobic blocks were synthesized independently and covalently connected by the copper (I)-catalysed alkyne-azide cyclo addition (CuAAC) "click" chemistry [50]. The copolymer's pKa can be readily tuned by altering the ratio of amino substituents. Similar to aforementioned UPS designing, a fluorescent cyanine dye (Cy5.5) was attached at the chain end of the amphiphilic copolymer to convert the subtle pH

variation into significant fluorescence intensity change. This study suggested that the ultra-pH sensitivity resulted from the reversible protonation of ionizable amines rather than the peptide backbone. It also in spired the design of degradable ultra-pH sensitive polymers.
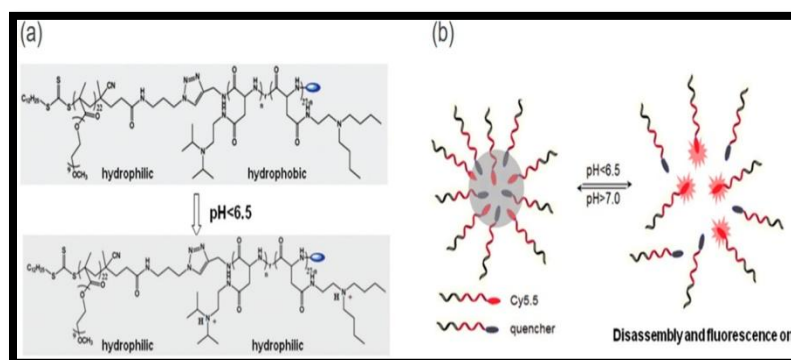


**Figure 4:** Design of ultra-pH-sensitive polypeptide micelles. (a) Structure of amphiphilic copolymers with ionizable tertiary amines and their transition at lower pH. (b) pH-triggered disassembly and fluorescence.

Natural macromolecules with ionizable amino acid residues have also been investigated for pH triggered delivery of imaging and therapeutic agents[51–55]. Engel man and colleagues have been working on the development of novel pH-responsive transmembrane peptides, pH low insertion peptide (pH LIPs), for basic research and translational applications in membrane biophysics and medicine (Figure 5)[56]. These pH-responsive peptides were derived from the C-helix of the protein bacterio rhodopsin[57]. pH LIPs spontaneously self-assemble into a helix structure and insert across the membrane upon exposure to acidic environment[58]. In physiological condition, where the pH is around 7.4, the ionizable acid residues of the pHLIP (red circles) stay negatively charged and the peptide will be weakly bound to the surface of membrane. Once encountering acidic condition like tumor microenvironment, carboxyl group will be protonated and neutralized. Increased lipophilicity (green circles) as a result of ionization drastically enhances the affinity of pH LIP to the hydrophobic inner core of the cellular membrane and triggers the formation of a helix and ensuing insertion across the membrane. When the protonatable carboxyl groups are exposed to the normal intracellular pH, pHLIP gets reversibly deprotonated and anchors in the membrane. The pH-responsive behavior of pHLIP can be easily modified by replacing ionizable aspartic acid residues with glutamic acid residues[60-61] or positively-charged lysine residues [59], or other protonatable amino acids [62].
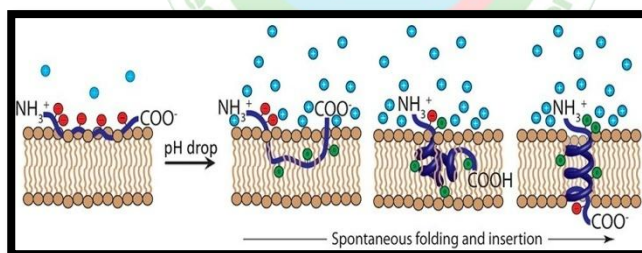


**Figure 5:** Mechanism of pH (Low) Insertion Peptide (pHLIP)

Insertion into the Cellular Membrane. In healthy tissue where the pH is around 7.4, the ionizable residues of the pHLIP (red circles) remain deprotonated and negatively charged, and the peptide resides at or near the hydrophilic surface of the cellular membrane. Upon exposure to acidic tumor microenvironment, the ionizable residues and negatively charged C-terminal carboxyl group of the pHLIP become neutrally charged (green circles). The protonation results in an increase in the hydrophobicity of the pHLIP, triggering the pHLIP to spontaneously fold into a helix and insert across the hydrophobic lipid bilayer of cell membrane, resulting in the formation of a transmembrane helix. Following internalization and exposure to cytosol with pH above 7, C-terminal ionizable residues are deprotonated again and anchor the pHLIP into the membrane.

Polyacids have also been extensively investigated for the design of pH-responsive nanoplatforms. Hyaluronic acid (HA) is a key component of the extracellular matrix and is known to bind to CD44 proteins as a surface receptor on cancer cells[63]. Kono and coworkers reported HAbased pH-sensitive polymer-modified liposomes for tumor-targeted delivery of chemotherapeutics [64]. Instead of simply using HA as targeting moiety, these authors introduced 3-methyl glutarylated (MGlu) units and 2-carboxycyclohexane-1-carboxylated (CHex) units for the design of a new class of pH-responsive polymers with transition pH around 5.4–6.7. Carboxyl group-introduced HA derivatives were prepared by reaction with various dicarboxylic anhydrides. Terminal alkyl chains served as anchor units inserting into the hydrophobic lipid bilayers of liposomes (Figure 6).
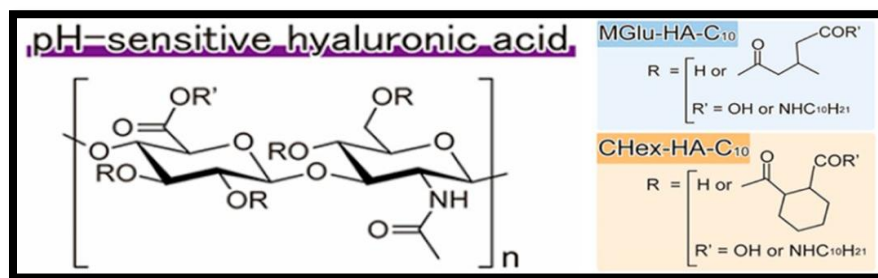
**Figure 6**: Structures of pH-sensitive modified hyaluronic acid derivatives.

## pH Responsive Dissociation Based on Acid-Labile Linkages

Polymers containing acid-labile or base-labile linkages can respond to the change of pH by degradation. Since the tumor microenvironment is slightly acidic compared to normal physiological environment, polymeric nanoparticles containing base-labile linkages have seldom be enused for cancer therapy and will not be covered in the perspective. In contrast, polymers with acid-labile linkages have been extensively utilized for the designing of anticancer drug delivery systems [65].

Hydrazone is one of the most explored acid-labile linkages used for acid-responsive dissociation release due to its easy synthesis and moderate sensitivity[66]. Incorporation of hydrazine into the backbone of polymers represents an ideal strategy for the design of tumor-targeted drug delivery
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systems. Nie group designed a pH-sensitive drug-gold nanoparticle system for tumor chemotherapy and surface enhanced Raman scattering (SERS) imaging (Figure 7)[67]. This multifunctional system comprised of poly (ethylene glycol), doxorubicin (Dox), hydrazone linker, and gold nanoparticles (Au–Dox–PEG). 3-[2-pyridyldithio] propionyl hydrazide (PDPH) was conjugated with Dox in methanol. PDPH acted as a pH-sensitive linker and introduced thiol groups to ensure the anchoring of drug conjugates onto the surface of gold nanoparticles. Gao and coworkers developed a pH responsive polypeptide–drug nanoparticles for targeted cancer therapy based on well-defined elastin-like polypeptides and acid-labile hydrazone linker[68]. Wang reported a hydrazone-based multifunctional sericin nanoparticles for pH-sensitive subcellular delivery of anti-tumor chemotherapeutics[69]
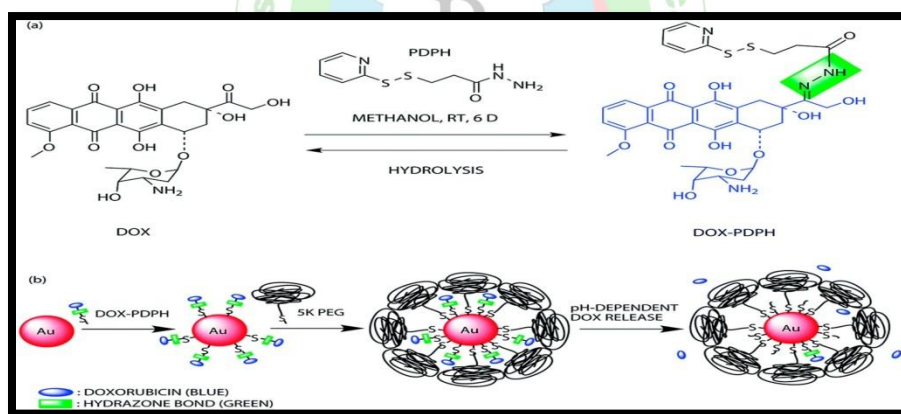


**Figure 7**: A pH-sensitive drug-gold nanoparticle system. (a) Chemical synthesis of the doxorubicinhydrazone linker conjugates (dox–PDPH). (b) Schematic illustration for the synthesis of the multifunctional drug delivery system and its pH-dependent doxorubicin release.

Acetal and ketal are also commonly used acid-labile linkages, which are very stable under basic conditions, but can be readily hydrolyzed to corresponding carbonyl compound (aldehyde and ketone) and alcohols through a caboxonium ion intermediate upon acidic cleavage[70]. Lu and coworkers reported a novel envelop-like mesoporous silica nanoparticle platform[71]. This system immobilized acetals on the surface of silica (yellow, left) before coupling to gate-keeper nanoparticle (purple, right) (Figure 8). At acidic pH, the acetal was effectively hydrolyzed to remove the gate keepers, allowing the escape of entrapped drug molecules. Liu et al. reported the facile fabrication of acid-sensitive polymersomes for intra cellular release of drug over several days[72]. The polymersomes compromising cyclic benzylidene acetals in the hydrophobic bilayers were

stable under neutral pH, whereas were hydrolyzed into hydrophilic diol moieties upon exposure to acidic pH milieu. The pH-triggered hydrolysis can be easily monitored by many experimental methods including UV/Vis spectroscopy and TEM. A novel class of acid degradable poly (acetal urethane) was also reported for the construction of acid-degradable micelles for delivery of hydrophobic anti-tumor therapeutics[73]. More recently, Wang group designed a new hyper branched amphiphilic acetal polymers for pH-sensitive drug delivery [74]. Under neutral conditions, the block copolymers self-assembled into well-defined core-shell micelles. This pH-induced acetal cleavage resulted in the drastic decrease of hydrophobicity and dissociation of micelles. De Geest and coworkers synthesized ketal-containing block copolymers

as pH-responsive nanocarriers for the hydrophobic anticancer drug paclitaxel (PTX) 75. The hydrolysis of the ketal groups in the block copolymer side chains at pH < 5

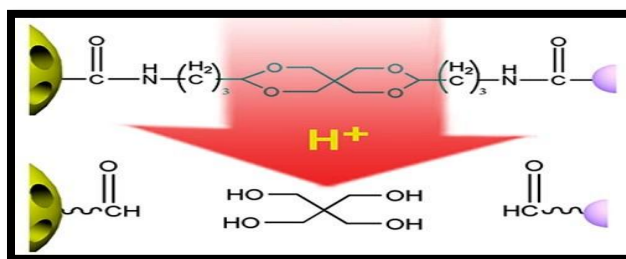lead to decomposition of the block copolymer nanoparticles and the PTX release.



**Figure 8:** Schematic illustration of the envelope-type mesoporous silica nanoparticle for pH responsive drug delivery.

Boronate esters, formed between a boronic acid and an alcohol, are stable at neutral or alkaline pH and readily dissociate to boronic acid and alcohol groups in a low-pH environment. Boronate esters have been widely employed to exploit pH-sensitive polymeric carriers for anticancer drug delivery. Messersmith et al. conjugated the boronic acid containing anticancer drug bortezomib (BTZ) to catechol-containing polymers via the boronate ester (Figure 9) [76]. Under neutral or basic condition, BTZ and catechol formed stable conjugates via boronate ester linkers, deactivating the cytotoxicity of BTZ. Upon exposure to

lower pH, the conjugates readily release free drugs. Levkin and coworkers reported a dextran-based pH-sensitive nanoparticle system by modifying vicinal diol of dextran with boronate esters. PH-triggered hydrolysis of ester linkers resumed the hydrophilic hydroxyl groups of dextran and destabilized the dug-encapsulated nanoparticles. Kim et al. reported a pH-sensitive nanocomplex bygrafting phenylboronic acid (PBA) onto the backbone of poly (maleic anhydride). Dox and PBA readily formed boronate esters following simple mixing.

**Figure 9**: Catechol-containing polymers conjugated the boronic acid containing anticancer drug bortezomib via acid-labile boronate esters. Boronate esters are
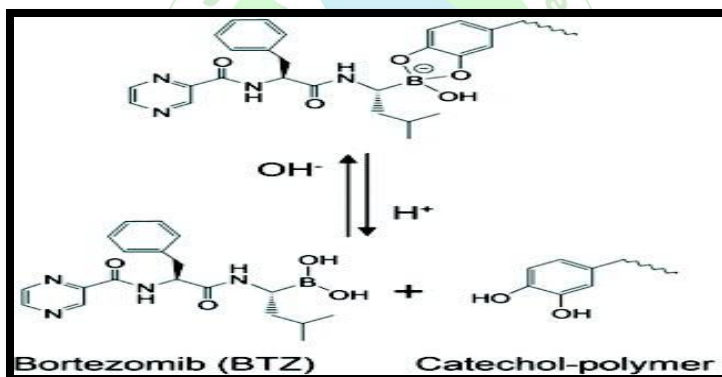


stable at neutral or alkaline pH and readily dissociate to boronic acid and alcohol groups in acidic environments to release the free active drug.

### Synthesis methods of magnetic nanoparticles

Methods based on preparation from solution allow the formation of magnetic NPs with precise controlled size and shape in a simple manner.

### Homogeneous precipitation

Homogeneous precipitation methods are used in order to achieve uniform particles. These methods have as basis the separation of the nucleation and growth of the nuclei. When the concentration of continuant species attains critical supersaturation, one short burst of nucleation appears and so the nuclei are synthesized. They can grow consistently by means of diffusion of the solutes from the solution on their surface, up to when they achieve their final size. These two phases must be distinct in order to attain monodispersity, meaning that once the growth process is established, nucleation must be avoided. However, uniform shaped nanoparticles have also been realized after numerous

nucleation events, the final uniform shape being attained by self-sharpening growth process[77].

### Coprecipitation

The coprecipitation method is probably the easiest and most efficient synthesis method used to achieve magnetic NPs. Iron oxides, magnetite or maghemite, are usually processed using stoichiometric mixtures of ferrous and ferric salts, in an aqueous environment. Magnetite can be converted into maghemite by means of air oxidation. In order to obtain magnetite spherical particles in solution, there are two principal synthesis procedures. The first one is based on ferrous hydroxide suspensions that are partially oxidized with various oxidizing agents. In the second method, stoichiometric mixtures of ferrous and ferric hydroxides are obtained in aqueous solutions, reaching homogeneous sized and spherical magnetite particles. It is likely to manage the particles size by tailoring the pH and the ionic strength of the precipitation medium. Using this method, the main asset is that a big amount of magnetic NPs can be synthesized.

However, the downside is that the particle size distribution cannot be controlled [77-78].

## Microemulsion methods

Water-in-oil (w/o) microemulsions are liquid solutions with properties as thermodynamic stability, isotropy, transparence and are also simple and versatile starting materials which can furnish nanosized particles. This type of systems consists of a continuous oil phase, in which dispersed assemblies of surfactant molecules can be found. In these assemblies of surfactant molecules, there are entrapped micro droplets of the aqueous phase. The limitation of particle nucleation, growth and cluster formation is given by the surfactant-stabilized microcavities. There have been conducted studies using this synthesis method, the result being magnetic NPs with an average size of 4 nm up to 12 nm and a standard deviation of 0.2 up to 0.3. These types of emulsions are used to synthesize super paramagnetic iron oxide nanoparticles with controlled size and shape. The main asset of this method is the controlled size of the NPs that can be obtained by managing the dimension of the aqueous droplets core.

## Polyol method

Polyol solvents, such as PEG, have unique properties: from the dielectric point of view, they behave as solvents capable to dissolve inorganic compounds; from their high boiling point of view, they present a large operating temperature range in the concern of synthesis of inorganic compounds. The polyol liquid is the solvent of the metallic precursor and the reducing agent. The metallic precursor can be either very soluble or lightly soluble in the polyol. The solution is then mixed up and heated to a given temperature. Non-aggregated and well-defined particles can be obtained by managing the kinetics of reactions in solution. The polyol method was the first technique that used noble metals (e.g., gold) and nickel, cobalt or copper. Recently, the method has widespread and was used to synthesize other materials, as iron based alloys. Non aggregated magnetite nanoparticles can be synthesized using the polyol process.

## High temperature and hydrothermal reactions

Dispersible magnetic iron oxide NPs can be obtained by the decomposition of Fe precursors in the proximity of hot organic surfactants. Hydrothermal synthesis of $Fe_3O_4$ is realized in aqueous media, in reactors with sustain high pressures and temperatures. There are two reactions that can result in the formation of ferrites: hydrolysis and oxidation of mixed metal hydroxides. The only difference between the two is that in hydrolysis, ferrous salts are used. The main characteristics that have an impact on the final product are temperature, time and the solvent. If during the reaction time is longer, the size range of the $Fe_3O_4$ powders is higher. Using thermal decomposition, hydrophobic magnetite particles were synthesized from Fe (CO) 5 in an octylether solution of oleic acid. Sol–gel reactions the sol–gel process uses molecular precursors that go through hydroxylation and condensation in a solution. The reactions are conducted at room temperature, thus additional heat treatments is needed in order to achieve the final crystalline shape. Solvent, temperature, concentration and pH are some of the parameters that influence in properties of the gel. This method can attain strict control over the particle size, monodispersity and predetermined structure. An example is the synthesis of maghemite NPs with a size range between 6 nm and 15 nm, after a heat treatment of the gels at high temperature (4000C) [78].

## Aerosol/vapor methods

Precise shaped and sized magnetic nanoparticles can be obtained using spray and laser pyrolysis. These methods have a high manufacturer rate that foresees a promising future for the synthesis of magnetic NPs used in vivo and in vitro applications. In spray pyrolysis process, a solid is obtained by spraying a solution in a succession of reactors. In these reactors, the aerosol droplets are subjected to evaporation of the solvent and solute condensation in the droplet. The following step is drying and thermolysis of the precipitation particle at higher temperatures. Finally, the results are microporous solids, from which in the end dense particles are formed. The shape and size of the final particles can be managed from the original droplets. Laser pyrolysis consists in heating a flowing mixture of gases with a continuous wave carbon dioxide laser. The laser initiates and maintains a chemical reaction. This method can manufacture small sized particles, with narrow particle size distribution and also an almost absence of aggregation. By using a one-step CO2 laser pyrolysis

## Sonolysis

Iron oxide can be synthesized by sonolysis of organometallic precursors. High temperature is generated by the fast collapse of the cavities (cavitation process) and ferrous salts are conversed into magnetite NPs.

## pH sensitive core-shell magnetic nanoparticles

In the last years, there had been an intense interest in the manufacturing of core-shell magnetic NPs. Core-shell magnetic nanoparticles can merge the magnetic properties given by magnetic NPs as the core and the properties of the shell, depending on the material[79]. Core-shell NPs have unique combined properties such as lower cytotoxicity, higher dispensability, biocompatibility and chemical and thermal stability. Occasionally, the shell does not only have the property of increasing biocompatibility, but also of improving the cores properties. The hydrophobicity of nanoparticles is an important aspect when the NPs are dispersed in aqueous media. Core shell nanoparticles have been intensively investigated in the field of cancer therapy. The core is coated with a convenient shell in the concern of increasing biocompatibility and pharmacokinetic properties in the human body. The anticancer agent is either attached or encapsulated in/on the core-shell complex. Higher surface leads to higher drug storing capacity. Surface modification must be made in respect of releasing the anticancer agent in the tumor site by means of changes in the pH values [80]. The pH value of damaged tissues, when affected by inflammation, infection or cancer is substantially different than the pH of healthy tissues. For example, if the tissue is subjected to a 60-hour inflammatory reaction, its pH value drops from 7.4 to 6.5. Specific targeting of pharmaceutical drugs in the tumor site

is highly important in cancer therapy [81]. In core-shell nanoparticles with directly connected functionalities, the shell must be made of organic or inorganic materials that are directly grown or connected to the magnetic core in order to achieve another performance apart from their magnetic one. Magnetic NPs have been widely used in biomedical applications that require high biocompatibility; therefore, surface functionalization is an essential requirement in the interest of making them applicable in this field. Multi functionalized nanocomposites consist of a chemotherapeutic agent (discharged by a pH sensitive mechanism), a specific ligand that can relate to tumor cells and iron oxide NPs as a core [82]. Even though iron oxides have many crystalline polymorphs, only magnetite ($Fe_3O_4$) and maghemite ($\gamma$-$Fe_2O_3$) are used in biomedical applications. Their surface chemistry and functionalization can also be easily fashioned. In order to improve drug delivery, adequate surface coating must be realized to become an integral component of a multifunctional magnetic NPs platform. To achieve this, an iron oxide core can be coated with organic materials (e.g., PEG), inorganic materials (e.g., gold) or oxides (e.g., silica) [83]. The magnetic polymer-coated NPs, loaded with specific tumor drug is guided to the desired location by means of an external magnetic field. When the magnetic field is removed, the nanovesicles will detect the cancerous cells by tumor recognition function and the drug will be released because of the change in pH (from physiological pH – 7.4 to endosomal pH – 5.3). The drug release can be accelerated by a magnetic field [84]. pH responsive polymers can modify their size in function of the changes in the pH of the surrounding environment, resulting in a expansion or a collapse, depending on the pH of the media. This behavior is due to the existence of specific functional groups in the polymer chains. The pH sensitive materials can be classified in two groups. In the first one there are polymers containing acidic groups, such as –COOH, which expand in basic pH (e.g., polyacrylic acid). The second one consists of polymers with basic groups, as –NH2, which swell in acidic pH (case of chitosan). pH dependent expansion of nanogels can also be used for the drugs loading. When the pH-sensitive nanosized gel swells, the permeability increases, thus allowing the encapsulation of NPs or the release of an already incorporated drug [85].

## Applications in cancer therapy

Cancer is known to be the leading cause of mortality worldwide. This cause is determined by the rapid and uncontrolled cell growth. The most used treatment to kill cancerous cells is chemotherapy. However, chemotherapy treatment comes with severe sides effects, because of its lack of specificity, affecting also healthy cells. In order to overcome the downsides of chemotherapy, an effective approach is the use of systemic nanomedicine with anticancer drugs. Presently, multifunctional nanoparticles platforms have been used as target drug delivery systems.

Magnetic nanoparticles coated with polymeric materials have higher stability, superparamagnetism and suitable biocompatibility as drug vesicles [86].

Doxorubicin (DOX) was used as an anticancer drug. The anticancer drug attached was DOX. It was shown that PAA and FA shell could encapsulate a big amount of DOX and showed remarkable efficiency for targeting [87].

Nanomaterials are intense researched because of their unique properties that make them promising for biomedical applications. Magnetic nanoparticles have super paramagnetic properties, meaning that when the magnetic field is removed, they can redisperse. Core-shell magnetite hybrid NPs have the advantage of high stability against oxidation and also, because of the polymeric shell, a great amount of drug can be encapsulated. Poly-2-dimethyl amino ethyl methacrylate (PDMAEMA) has excellent properties, such as biocompatibility, hydrophilicity and pH responsivity, which make them suitable for medical and pharmaceutical studies. [88]

The silica shell preserves the magnetism of $Fe_3O_4$. However, $Fe_3O_4@SiO_2$ cannot load drugs properly, so the need of a more complex system is desired. Multifunctional hybrid NPs were obtained by attaching to the silica coating the biocompatible block polymer polyethylene glycol-block-polyaspartic acid (PEG-b-PAsp). This enabled the stabilization of the magnetic NPs and also avoided absorption. PAsp was used in order to encapsulate the therapeutic drug (DOX) via electrostatic interaction. This kind of hybrid NPs showed great potential applications in cancer therapy as targeting drug delivery carriers[89].

Nanoparticles smaller than 200 nm will avoid the RES recognition when coated with PEG, a hydrophilic and biocompatible polymer. An example of such NPs is the PEG-b-poly-D, L-lactide, which contain encapsulated DOX and a superparamagnetic NPs cluster. The used cytostatic is adriamycin (ADR), encapsulated into the PGMA-coated core by simply blending them in an aqueous solution at physiological pH. When reaching a pH lower than 5.5, the drug was released. This formula showed low cytotoxicity because of the MPEG shell [90].

When the pH value was 7.4, less than 35% of the drug was released in 50 hours; when the pH value dropped to 5.5, 80% of the drug was released in the same amount of time. To improve targeted drug delivery in cancer therapy, a system consisting of titanium oxide encapsulated iron oxide NPs ($Fe_3O_4@TiO_2$) have been developed. An anticancer drug, DOX, was loaded in the core-shell structure. $Fe_3O_4@TiO_2$ nanoparticles display pH sensitive release of DOX in the desired area. These NPs could be used in the treatment of cancer with chemo-sonodynamic therapy [91-92].

## CONCLUSIONS

The state-of-the-art of pH-responsive drug delivery using mesoporous nanoparticles has been deeply revised. These stimuli-responsive nanocarriers are based on the small variations in pH between healthy and diseased areas along the body. Those variations are used to trigger the release of the cargo through different mechanisms. We have considered three different approximations of pH-responsive nanocarriers. The host-guest interactions have been shown to be useful to retain the drugs at physiological pH. However, it would be desirable to minimize the amount of

drugs released outside the target area despite the electrostatic interactions. Regarding the pH-responsive nanocarriers, it has been shown in this review that it is possible to design hybrid nanoparticles capable of triggering the release in very specific situations through the subtle changes in pH. However, it is still difficult for all of the nanocarriers injected to reach the diseased area. Then, future work should be directed toward synthesizing smart pH-responsive nanocarriers with enhanced targeting ability, capable of avoiding the different barriers present in the body and accumulating only in the diseased tissues to increase the efficacy of the therapy.Nevertheless, recent advances in the polymer design, structure-property correlation, mechanistic understanding, and applications of a multitude of pH-sensitive nanomaterials reviewed here provide general guidelines for future rational design of more effective pH-responsive nanomaterials for cancer diagnosis and treatment.

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