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A Beacon for Gynecological Cancers Patients: pH-Sensitive Nanomedicine

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Abstract

Emergence of various nanoscale drug carrier platforms as Drug Delivery Systems (DDS) has revolutionized the field of medicine. Nonetheless, the side-effects due to non-specific distribution of anticancer therapeutics in normal, healthy tissues remain to be a prime pitfall in curing cancers. Therefore, to achieve a better therapeutic efficacy the use of a target-specific delivery, combined with a stimuli-responsive nanocarrier system, particularly pH-sensitive nanosystems offer an attractive strategy. Targeted drug delivery through pH-sensitive nanosystems offer the potential to enhance the therapeutic index of anticancer agents either by increasing the drug concentration in tumor cells and/or by decreasing the exposure in normal host tissues. Therefore, nanoscale-based drug delivery through pH-sensitive nanosystems seem to be a boon for treating gynecological cancers (as well as other cancers) without side-effects or with least harm to normal healthy tissues.

Introduction

A hope of successful treatment of cancers without side effects has challenged oncologists and onco-scientists since decades. Burgeoning research in nanotechnology and the depth of understanding in gynae-oncological pathophysiology at the cellular and molecular levels have led to the development of different well-tailored nanosized carriers for drug loading and controlled delivery at the targeted site. In recent years, nanosized carriers (nanocarriers) have gained attention as unique drug delivery agents due to following qualities: (i) they have abilities to incorporate payloads with different solubilities [1], (ii) they improve the *in vivo* Pharmacokinetics (PK) of drugs [2], (iii) they enhance bioavailability (i.e. the drug stability and longevity in the blood circulation with or without additional structural modifications) [3], and (iv) they modify the carriers with targeting ligands on their surface for tumor tissue or cell-specific delivery to minimize side-effects on healthy cells/tissues [4]. Some of the nanocarriers developed till today are liposomes, dendrimers, polymeric Nanoparticles (NPs), gold or other metallic NPs, inorganic NPs made of iron oxide, quantum dots etc [5-7]. Few of them possess unique nature of stimuli-responsiveness. Such stimuli-responsive nanocarriers have emerged as an "intelligent" or "smart" DDS. Thus, these nanocarriers have exhibited myriads of successful applications in comparison with conventional DDS.

The main purpose of developing nanomedicine and nanotherapies is to avoid damage to healthy organs. So, this innovative approach seems to have tremendous potential to improve the effectiveness of nanomedicine to treat clinical tumors with null side effects [8]. There are several nanomaterials which have been found to be responsive to external (*viz.*, light, ultrasound) and internal stimuli (*viz.*, pH, redox potential, temperature), and have been utilized for cancer therapy and simultaneous diagnosis i.e. theranostics [5,9,10]. Among the various stimuli-responsive nanosystems, pH-stimuli mode is regarded as the most general strategy because of solid tumors acidosis. When exposed to weakly acidic tumor microenvironment, drug carrying pH-responsive nanoplatforms can generate physicochemical changes in their structure and surface characteristics, causing drug release or contrast enhancement at a particular pathological site [11,12]. This ease of controlled drug delivery at the desired site has incepted the preliminary idea of developing pH-sensitive drug delivery nanosystems. Moreover, the pH-responsive NPs are one of the most extensively studied stimuli-responsive nanosystems. This is due to its sensitivities to the changes in pH condition at the tumor or diseased tissue site [13,14].

Generally, pH-responsive nanoparticles are fabricated either using acid-sensitive linkers or ionizable groups [15]. A variety of pH-sensitive nanoparticles have been designed in recent decades and have characteristic functionalities in the molecular structure, where pKa (negative logarithm

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of the acid dissociation constant) values are close to the tumor interstitial pH. When these nanoparticles reach tumors where the microenvironmental pH is slightly acidic, a pH-dependent structural transformation occurs. The acidic environment at the tumor site triggers the protonation of pH-sensitive moieties, thereby disrupting the hydrophilic-hydrophobic equilibrium within the nanoparticle, in turn causing structural transformation and the release of therapeutic cargo loaded inside.

Despite of few problems associated with nanomedicine, pH-sensitive nanoparticle-based DDS remain as a potential strategy for cancer therapy. Some nanoparticle formulations for cancer treatment have been already approved by regulatory agencies. These formulations exert fewer adverse effects than unmodified or bare drugs [16]. Therefore, in the interest of brevity, this review article simply retrospects and compiles only pH-sensitive nanosystems among other internal stimuli-responsive systems. Some of the pH-sensitive nanosystems retrospected here are certainly not yet directly used for treating gynecological tumors but paves the way for employing them for treating gynecological cancers with some strategic modifications depending on tissue types.

pH-Sensitive nano-systems

Generally, physiological pH remains 7.4 (weakly basic) but the subcellular compartments *viz.*, endosomes and lysosomes exhibit remarkably lower pH of about 5 to 6 or 4 to 5, respectively. Therefore, significant lower pH in subcellular compartments has been used as a route for delivering anticancer drugs by the pH-stimulated release from endocytosed drug carriers [17]. Since the inception of pH-sensitive NPs, myriads of innovative approaches for cancer treatment have come into light. Past decades have witnessed synthesis and utilization of various pH-responsive nanosystems *viz.*, liposomes, block copolymers, polymeric micelles, polymerosomes, polymer-drug conjugates, dendrimers, nanogels, and multiple core shell complexes etc [18]. These are briefed as follows

1. Liposomes: They are phospholipid vesicles consist of one or more concentric lipid bilayers enclosing discrete aqueous spaces. They can entrap both lipophilic and hydrophilic compounds thus employed for delivering diverse range of drugs. Moreover, its large aqueous center and biocompatible lipid exterior permits the delivery of different macromolecules, *viz.*, DNA, proteins and imaging agents [19]. Thus, liposomes are the most common and widely sleuthed nanocarriers for targeted drug delivery due to their flexible physicochemical and biophysical properties [19]. Pegylated liposomal Doxorubicin (DOX: A tumor-specific peptide and chemotherapeutic agent) has been observed to be efficient in breast cancer treatment both as monotherapy and in combination with other chemotherapeutics [20]. In 2016, Silva and colleagues have reported pH-sensitive long-circulating liposomes for selective delivery of DOX into tumor [21]. Karanth and Murthy [22] have extensively analyzed previous reports on the cytosolic delivery of the drugs through pH-sensitive liposomes and suggested that pH-sensitive liposomes were more efficient in delivering anti-cancer drugs than conventional and long-circulating liposomes due to their fusogenic property. Recently, a team of investigators have lucidly elaborated the developmental and applicability status of pH-sensitive liposomes in cancer treatment and concluded it very successful as pharmaceutical carriers for intracytoplasmic delivery of antineoplastic drugs [23]. Few investigators have reported pH sensitive coiled coils and their incorporation into the liposome as triggers for the controlled release of encapsulated drugs. From the drug encapsulated liposome internalization experiments with cancer cells; they revealed the enhanced release and accumulation of drugs in the acidic lysosomal compartments in comparison with liposomes without coiled coils [24]. In an attempt to develop targeted drug delivery systems with cancerous cell-specificity and controlled release function inside cancer cells, Miyazaki and colleagues have designed Hyaluronic Acid (HA)-based pH-sensitive polymers as multifunctional polymers. These polymers exhibited not only pH-sensitivity but also targeting properties to cells expressing CD44 (a cancer cell surface marker). They observed that HA-derivative modified liposomes can be efficiently used for cell-specific intracellular drug delivery [25]. Further research studies on the therapeutic and clinical aspects of pH-sensitive liposomes are needed to enable their commercial utility in gynecological cancer treatment.

2. Block copolymers: Amphiphilic block copolymers are self-assembled into polymeric micelles (10 nm to 100 nm in diameter) in aqueous media. These micelles possess a well-defined hydrophobic core and a hydrophilic corona. Block copolymer micelles can thus significantly improve the solubility of the hydrophobic drug formulated in the core; whereas, the densely packed corona consists of the hydrophilic end of the block copolymer, can protect the micellar system from the RES elimination by reducing the interaction with serum proteins and renal filtration [26]. The pH-sensitive block-copolymers allow for controlled micelle dissociation and triggered drug release in response to the acidic pH of tumor tissue.

The pH-sensitive polymeric micelles assembled from hyperbranched amphiphilic block copolymer loaded with DOX have exhibited remarkable cytotoxicity against HeLa cells in a dose- and time-dependent manner. Thus, proved to be a potential carrier candidate for pH-responsive drug delivery in treating cancer [27]. Moreover, a dual-pH-sensitive micelle loaded with Paclitaxel (PTX, a chemotherapeutic agent) has been also proved to be a potential nanocarrier for effective metastatic tumor therapy without significant toxicity [28]. Poly(ethylene glycol)methyl ether acrylate-block poly (L-lysine)-block-poly (L-histidine) triblock co-polypeptides were synthesized for pH-responsive drug delivery. Such nanoparticles were found to be stable at physiological pH (7.4) but were dramatically destabilized in acidic pH due to the presence of pHis blocks [29]. The pH-induced destabilization of the nanoparticle enabled the controlled release of DOX, followed by a dose-dependent cytotoxicity in murine cancer cells. Zhang et al. [30] have reported a series of DOX-loaded pH-responsive poly(ethylene glycol)methyl ether-b-[poly lactic acid-co-poly (β-amino esters)] [MPEG-b-(PLA-co-PAE)] block copolymer micelles as drug delivery carriers for targeted cancer therapy with sustained release. Investigations carried out by Zhou et al. [31] have suggested that the polymeric micelles comprising of Polyethylene Glycol (PEG) and a Polymethacrylamide [PEG-b-PMEA] diblock copolymer could be useful for pH-responsive delivery of poorly soluble anticancer drugs. The pH-sensitive copolymer *viz.*, methoxy poly (ethylene glycol)-b-poly (hydroxypropyl methacrylamide-g-α-tocopheryl succinate-g-histidine) (PTH) forming micelles in aqueous solutions were used for co-delivery of therapeutic agents, DOX and α-TOS (α-tocopheryl succinate) in tumor cells. In this combination therapy, the micelles enabled the rapid release of both DOX and α-TOS when the pH declined from 7.4 to 4.5 in tumor tissues [32]. Mozhi et al. [33] have displayed a synergistic antitumor effect of the combination of anticancer drug Docetaxel and the therapeutic peptide [D(KLAKLAK)2] in an MCF-7 cell line using a pH-sensitive copolymer

viz., poly(β-amino esters)-poly (ethylene glycol) conjugated with the dual-targeting proapoptotic peptide CGKRKD (KLAKLAK)2. In which, CGKRK peptide efficiently transported D(KLAKLAK)2 towards mitochondria to trigger mitochondria-dependent apoptosis [33]. Few investigators have reported synthesis of pH-sensitive copolymer through bridging Poly (2-Methacryloyloxyethyl Phosphorylcholine) (PMPC) block and Poly (D, L-Lactide) (PLA) block by a benzoyl imine linkage (Blink). These biomimetic micelles (PLA-Blink-PMPC) were prepared as carriers for PTX delivery. Such pH-triggered drug release behavior in synchronization with tumoral acidic conditions was found to be helpful for improving the utilization of drug and facilitating antitumor efficacy [34]. Furthermore, Wang et al. [35] exhibited antitumor efficiency of DOX-loaded micelles. In which, ortho ester degradation of DOX-loaded, pH-sensitive micelles consisted of triblock copolymer PEG-block-poly (ortho ester urethane)-block-PEG (PEG-POEU-PEG) were found to notably accelerated at pH 5.0 due to its pH sensitivity. Last year, few investigators have reported a chemo-photothermal therapy of cancer cells by using gold nanorods (AuNRs)-based pH-sensitive thiol-ended triblock copolymer micelles (PAA-b-PDMAEMAQ-b-PCL-SH), in which AuNRs at polymer was loaded with Methotrexate (MTX) as an anticancer drug [36].

3. Polymeric micelles: They are self-assembling nano-constructs of amphiphilic copolymers and are widely regarded as efficient nano-carriers for myriads of applications, including drug delivery, diagnostic imaging etc. These became feasible because of their variety of favorable properties *viz.*, biocompatibility, and bioavailability, capacity to effectively solubilise myriads of poorly soluble drugs, enhancing release profile of the incorporated pharmaceutical entities, ability to accumulate in the targeted tissue based on the EPR effect and ability to attach various targeting ligands to the micellar surface. The combination of these approaches has been found to further improve specificity and efficacy of micelle-based drug delivery to promote the development of smart multifunctional micelles [37]. Ko et al. [38] have evaluated anti-tumor activity of pH-responsive polymeric micelles made up of Methyl Ether Poly(Ethylene Glycol) (MPEG)-poly (β-amino ester) block copolymers, by injecting the DOX-loaded polymeric micelles into tumor-bearing mice. These micelles notably suppressed tumor growth and prolonged survival of the tumor-bearing mice, compared with mice treated with free DOX. Giacomelli et al. [39] have reported pH-triggered micelles composed of a pH-responsive PDPA [poly(2-diisopropylamino)ethyl methacrylate] inner core and a PEO [Poly(Ethylene Oxide)] outer shell as a promising drug delivery system for the cancer therapy. In which pH-responsive PDPA core was loaded with PTX. *In vivo* evaluation of DOX-loaded pH-sensitive polymeric micelles made up of poly(L-histidine-co-L- phenylalanine -b-PEG and poly(L-lactic acid)-b-PEG-folate was carried out in Multidrug-Resistant (MDR) ovarian tumor- xenograft mice. It was observed that the drug-carrying micelles were exhibiting enhanced intracellular DOX-delivery by circulating for long-time (i.e. enhanced bioavailability) and accumulating at tumor-selective sites. Thus, they exhibited enhanced cytotoxicity to tumor cells only, sparing the normal healthy cells [40]. Wang et al. [41] have shown that the PTX loaded pH-responsive Poly(ethylene glycol)-b-poly(D,L-lactide)-b-poly(β-amino ester) [PELA-PBAE] micelles might have the potential utility in the metastatic breast tumor therapy. In another study, the polymeric micelles incorporated with cisplatin were prepared by complexation between cis-dichlorodiammineplatinum (II) (CDDP) and hydrophilic poly(L-glutamic acid)-b-poly(2-methacryloyloxyethyl phosphorylcholine) (PLG-b-PMPC) diblock copolymers. Investigators observed the sustained release of CDDP from the micelles was faster in acidic pH (5.0-6.0) than the physiological pH 7.4. Thus, CDDP-loaded polymeric micelles were developed for targeted cancer therapy to reduce the detrimental side effects of cisplatin CDDP [42]. Zhou et al. [43] have reported a pH-responsive pentablock copolymer made up of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)] conjugated poly (β-amino esters) (DSPE-b-PEG-b-PAE-b-PEG-b-DSPE) was able to self-assemble into polymeric micelles. These DOX-loaded polymeric micelles displayed pH-triggered high toxicity to tumor cells and HeLa cell lines whereas the copolymer had negligible cytotoxicity. Thus, these pH-sensitive micelles have the potential to be used for cancer chemotherapy with controlled release. Das et al. [44] and Zhou et al. [45] have lucidly elaborated the current advances in the development of pH-responsive polymeric micelles/nanoparticles, their mechanisms of action, and applications in chemotherapy, diagnostic imaging, and their delivery strategies and provided their future perspectives. This is yet to be sleuthed in human cells and gynecological tissues.

It is well understood that, among amino acids, Histidine (His) is an only essential amino acid having imidazole group. The presence of lone-pair electrons on the unsaturated nitrogen of this group confers pH-sensitivity to Histidine. Therefore, poly(Histidine) (pHis) has been extensively used for the fabrication of pH-sensitive drug delivery nanosystems. Uthaman et al. [29] have reported a variety of pHis-based polymeric micelles for the delivery of DOX [15,46-48]. In addition to these, nanocarriers composed of amphiphilic, biocompatible chitosan polymeric micelles were used to deliver Nonsteroidal Anti-Inflammatory Drug (NSAID) Ibuprofen in breast cancer therapy. It was observed to possess potential anti-tumor activity, while avoiding side-effects on normal, healthy tissues [49]. The pH-responsive nanoparticles combining Ibuprofen with chemotherapy agents have provided a novel nanoparticle system for both primary and metastatic tumor treatment [50].

Targeted efficient delivery and therapeutic efficacy of DOX have been found to be significantly increased by using a stepwise pH-responsive nanodrug delivery system [51]. This study has provided a promising strategy for efficient delivery of other antitumor agents. Similarly, some more nanocarriers like polymeric micelles, liposomes and solid NPs have been developed for hydrophobic as well as hydrophilic drugs for effective therapy of cancer [52-56]. Last year, some investigators have revealed the intracellular pH-responsive nanoparticles of hyaluronic acid which can provide insights into the design of potential prodrugs for the cancer therapy [57]. Hydroxyapatite coated iron oxide nanoparticles and pH sensitive Sodium alginate have been developed for controlled release of hydrophobic drugs [58]. Yandan et al. [59] have shown that multifunctional sharp pH-responsive nanoparticles made up of Poly(2-(Diisopropylamino)ethyl methacrylate) (PDPA) polymer have great potential to serve as a new generation nanomedicine for effective breast cancer treatment

4. Polymersomes or polymeric vesicles: They are preferably prepared from amphiphilic, biocompatible and biodegradable polymers [60]. They have the potential to be versatile drug delivery systems because of their tunable membrane formulations, stabilities *in vivo*, various physicochemical properties, controlled release mechanisms, targeting abilities, and capacities to encapsulate varieties

of drugs etc. [61,62]. The pH-sensitive polymersomes have been developed to quickly respond to small changes in the environmental pH of tumor's microenvironment [60,63]. Following pH alteration, the pendant acidic (carboxylic acids/sulfonic acids) or basic groups (amine) undergo protonation or deprotonation. Consequently, the structural transition induces formation/deformation of polymeric vesicles, which confers a higher therapeutic index as a result of the fast release of therapeutics at the target site. However, the major obstacle to the application of pH-sensitive polymersomes is the slow response to the stimulus, resulting in a slow drug release, which eventually induces drug resistance in the adjacent cells. Therefore, polymersomes need to respond quickly as a result of the decreased pH at pathological sites. Thus, pH-responsive polymersomes need to be further designed to carry, deliver, and control the release of therapeutic agents to the tumor tissue by relying the low pH in the vicinity of tumor tissues [60,63]. Anajafi et al. [60] have explicitly elaborated recent developments of polymersomes. Their utilities in treating gynecological cancers are yet to be sleuthed.

5. Polymer-drug conjugate: (a) *Dendrimers or dendritic molecules* are highly branched with a central core, nanosized, and symmetric molecules with well-defined, homogenous and monodisperse structure with diameter 2 nm to 10 nm. They are classified by its form as polymers, hyperbranched polymers or brush-polymers and also classified by their molecular weight as low or high molecular weight [64,65]. Dendrimer act as a carrier for the delivery of drug to tumor by encapsulation or conjugation. Among polymer-drug conjugates, most widely studied dendrimers to date are non-biodegradable, cationic amine-terminated Poly-Amidoamine (PAMAM) dendrimers [66]. Drug delivery to tumor site is mostly accomplished through PAMAM, Poly (Propylene Imine) [PPI], and Poly (L-lysine) [PLL] dendrimers by either passive or active targeting [64]. Wen et al. [67] have explained the multifunctional dendrimer-modified multi-walled carbon nanotubes for targeted and pH-responsive delivery of DOX into various types of cancer cells. In 2018, Zhang et al. [68] have reported the development of pH-sensitive multifunctional DOX-conjugated PAMAM dendrimers as a unique platform for targeted cancer chemotherapy. Some other investigators have presented the construction of pH-responsive multifunctional dendrimer-based theranostic nanosystem (in which Gold nanoparticles conjugated with DOX were entrapped in dendrimer) to be utilized for simultaneous chemotherapy and Computed Tomography (CT) imaging of various types of cancer cells [69]. Dendritic polyester system based on monomers 2,2-bis(hydroxymethyl)propionic acid attached to DOX or hydroxyl-terminated generation 4 PAMAM in conjugation with PTX through a union with succinic acid have shown great anticancer activity against ovarian cancer cells [65]. However, at present the dendrimers used as drug-carriers do not satisfactorily meet the necessary characteristic of an ideal dendrimer for targeted drug delivery. However, the development and study of new dendrimers drug-carriers continues to be an important tool in the cancer therapy.

(b) *Acid-responsive polymers* have provided enhanced endosomal delivery of drugs. In the acidic microenvironment, acid-sensitive linkers have provided tools for targeted intracellular drug release. Hydrazone and cis-aconityl linkers are two types of acid-sensitive linkers which have been commonly used for this purpose. Both are relatively stable at physiological pH and can release the bound drugs only under low pH conditions. The hydrazone linker gets rapidly cleaved under low pH conditions (which occur in endosomes, lysosomes and tumor tissue). Through the hydrazone linker, the drug was found to be released in the acidic tumor microenvironment or in the acidic organelles after cellular uptake by endocytosis [70-75]. Some more sleuthed polymer-drug conjugates containing hydrazone linkages are HPMA-DOX, PEG-DOX [76,77], PEG-epirubicin and PEG-PTXL [78,79]. Hydrazone linked acid sensitive PEG-based drug delivery in lysosomes was also studied by Zhu et al. 2012 [74]. They found that Gemcitabine (GemC18) in the acid-sensitive micelles was more toxic toward cancer cells than acid-insensitive micelles. There are reports of a pH-sensitive hydrazone bridged and peptide-guided prodrug incorporating DOX for targeted ablation (removal of harmful parts of the body) of cancer cells with least cytotoxicity on normal healthy cells [80]. The pH-sensitive N-(2-hydroxypropyl) methacrylamide-DOX (HPMA-DOX) conjugates bearing an acid-responsive hydrazone linker in their structure have also been widely studied as anticancer drug delivery systems. They have been found to significantly increase therapeutic efficacy in different *in vitro* and *in vivo* cancer models. Liao et al. [57] have reported the synthesis of tumor targeting and pH-responsive nanoparticles for the enhanced delivery of DOX. The nanoparticles were prepared through the covalent bonding of DOX to Hyaluronic Acid (HA) backbone by hydrazone linkage. In aqueous solution, Hyaluronic Acid-hydrazone linkage-Doxorubicin (HA-hyd-DOX) could self-assemble into nanoparticles. Active targeting of the nanoparticles was achieved through receptor-mediated binding of HA to CD44, which is over expressed in most cancer cells. Studies on polymers that use cis-aconityl linker in designing anticancer drug delivery systems included HPMA-DOX [81], polyamidoamine-DOX [82] and Polyamidoamine (PAMAM)-DOX [83]. Furthermore, acid-sensitive cis-aconityl linked Polyethylene Glycol-Chitosan (PEG-CS) micelles were found to have a greater Docetaxel loading capacity, less cytotoxicity toward normal cells, enhanced cellular uptake and better accumulation in tumor tissue compared to acid-insensitive PCS micelles (PEG directly linked to CS) [84]. Moreover, the pH-responsive NPs have also been developed by conjugating nanocarriers with some other acid-labile linkages such as orthoester [85,86], imine [87,88], phosphoramidate [89], whose hydrolysis ensured rapid release of the drug at the targeted tumor.

(c) *Zwitterionic polymers* incorporated nanoparticles have been designed to demonstrate a pH-dependent change in surface charge. One of the most commonly investigated systems is based on zwitterionic polymers, as they have cationic and anionic groups that control surface charge in response to pH. In acidic pH, these zwitterionic polymers have a positive charge, and in basic pH, they have a negative charge. However, when these zwitterionic polymers are in neutral pH, they are overall neutral with balanced populations of positive and negative components and they become more hydrophobic. However, upon entering tumor cells, the balance between positive and negative charges alters and thereby causes conformational changes, facilitating drug release in tumor cells. Kang et al. [90] have reported the fabrication of tumor microenvironment responsive theragnostic with a pH-dependent fluorescence turn on/off property. The nanoparticles were constructed by encapsulating a photothermal dye (IR 825) in the carbonized zwitterionic polymer. Before accumulating in the tumor site, these nanoparticles displayed quenching of fluorescence due to the hydrophobic interaction with neutral pH and π-π stacking. The slight change in the pH in TME enabled the charge of the nanoparticles to be altered, leading to the release of IR 825 and recovered fluorescence. These types of nanoparticles can simultaneously be used for diagnosis and

photothermal therapy.

6. Multiple core shell complexes: The pH-responsive drug encapsulation and release from multiple core-shell nanoparticles become feasible due to the presence of polyelectrolyte multilayers [91]. Huang et al. [92] first synthesized Gd_2O_3:Yb_3^+:Er_3+, a functionalized mesoporous silica nanoparticle core, which was then coated by multi-layers of polyelectrolytes. DOX was then loaded onto the polyelectrolyte shell. The resulting DOX-loaded core-shell nanoparticles exhibited more than 60% DOX release within 72 h at pH 5.2. *In vitro* cytotoxicity studies on MCF-7 breast cancer cells showed that DOX-loaded nanoparticles exhibited higher cytotoxicity than the free DOX. Tian et al. [93] synthesized an azide-terminated diblock copolymer from Oligo(Ethylene Glycol) Methyl Ether Methacrylate (OEGMA), 2-(Diisopropylamino)ethyl Methacrylate (DPA), and Glycidyl Methacrylate (GMA). The resulting copolymer was then functionalized with DOTA (Gd) and 4-(prop-2-ynyloxy) benzaldehyde and the resulting copolymers were further co-assembled into mixed micelles. The presence of GMA moieties inside the cores enabled encapsulation of tetrakis [4-(2-mercaptoethoxy) phenyl] ethylene (TPE-4SH), and thus the resulting micelles were capable of MR and fluorescence dual imaging. Moreover, these micelles were surface-conjugated with pH Low Insertion Peptide (pHLIP), which enabled them for selective targeting toward tumor tissues and *in situ* Camptothecin (a cancer drug) release, confirmed by *in vivo* MR images of tumor-bearing BALB/c nude mice. Ray et al. [91] and their collaborators have synthesized a Unibody Core-Shell (UCS) nanoparticle using a polymer platform formed by resorcinol and 1,3-phenylenediamine monomers. In this synthesis, Gd_3^+ was first conjugated to the polymer backbone to form the Gd-core, and then DOX was encapsulated within the shell surrounding the Gd-core. Resorcinol was chosen as one of the components in the core. 1,3-phenylenediamine was chosen as the shell unit for its capability for pH-controllable release. *In vitro* and *in vivo* studies of UCS-Gd-DOX as an innovative theranostic nanoparticle showed that the DOX in the shell is effectively and selectively released in tumor acidic environments (pH 5.5). *In vitro* pH-dependant release of DOX after 2 h was found to be <5%, 10%, 55%, 75%, and 80%, at pH 8.0, 7.0, 6.0, 5.0, and 4.0, respectively. Enhanced drug release from pH 7.0 to 6.0 verified the potential of UCS-Gd-DOX for targeted therapy towards malignant tumor tissues. In addition, *in vitro* T1-weighted MR imaging studies also reflected the pH-switchable MR contrast capability of UCS-Gd-DOX. The pH-responsive design of the UCS nanoparticle not only improved the MRI contrast at the tumor site with respect to other tissue/organs, but also successfully suppressed growth of subcutaneous human cervical cancer in mouse xenograft models. Therefore, theranostic nanoparticles with Gd-conjugation and DOX-doping can be synthesized and further applications of UCS-Gd-DOX in the field of cancer treatment can be anticipated [91].

There are reports of **pH-sensitive magnetic nanoparticles** sleuthed for targeted anticancer drug delivery. In early years of this decade, a magnetic and pH dually responsive nanocarrier with multilayer core-shell architecture was constructed. In which, the Fe_3O_4@SiO_2 nanoparticles acted as a superparamagnetic core used to target the drug loaded nanocarriers to the pathological site. Meanwhile, the mPEG [α-methoxy poly (ethylene glycol)] and PBLA [poly(benzyl-L-aspartate)] segments served as a pH-sheddable hydrophilic corona and a hydrophobic middle layer used to load the drug DOX *via* hydrophobic interactions. This system appeared to be highly promising for the targeted intracellular delivery of hydrophobic chemotherapeutics in cancer therapy [94,95]. In 2017, Karimi et al. [96] have brought in light a pH-sensitive magnetic nanoparticle system for Methotrexate (MTX) targeting of tumor. In another study, Wu and his colleagues have performed *in vitro* evaluation of magnetic nanocomposites (Fe_3O_4@LDH-MTX) [in which Fe_3O_4 nanoparticles acted as magnetically responsive carriers and the coating layer of Layered Double Hydroxide (LDH) was used as a storehouse for MTX] as MTX delivery system for targeted anticancer therapy. They have observed its excellent pH-sensitivity and ~85% of MTX was released within 48 h at pH 3.5 *via* the co-effect of dissolution of LDH layer and ion-exchange. This study has revealed that the Fe_3O_4@LDH-MTX would be a competitive candidate for sustained, controlled release and targeted delivery of MTX because Fe_3O_4@LDH-MTX exhibited high anticancer activity with minimal toxicity to normal cells [97]. In addition to these reports, a pH-responsive nanoplatform made up of a yolk-like Fe_3O_4@Gd_2O_3 and functionalized by PEG and folic acid, has been documented to be a potential nanotheranostic for tumor targeted T_1-T_2 dual-mode Magnetic Resonance Imaging and chemotherapy using Cisplatin and HeLa cells [98]. Last year, pH-sensitive magnetic composite nanoparticle was prepared by double water-in-oil-in-water (W/O/W) emulsion using acetylated β-cyclodextrin as a pH-sensing material and Fe_3O_4 as a component to realize magnetic response. Its *in vitro* evaluation was performed for drug loading and release behavior [99]. This type of study can be also extended for treating gynecological tumors. In a review, Lungu et al. [100] have explicitly elucidated the utility of pH responsive core-shell magnetic nanoparticles in diagnosis and treatment of oncological diseases. Those NPs were: magnetite@silicondioxide (Fe_3O_4@SiO_2), Fe_3O_4@titanium dioxide (TiO_2), beta-thiopropionate-Polyethylene Glycol (PEG)-modified Fe_3O_4@mSiO_2, Fe_3O_4 NPs core coated with SiO_2 with an imidazole group modified PEG-polypeptide (mPEG-poly-L-Asparagine), Polyacrylic Acid (PAA) and folic acid coating of the iron oxide NP core, methoxy polyethylene glycol-block-poly methacrylic acid-block-poly(glycerol monomethacrylate) (MPEG-b-PMAA-b-PGMA) attached by a PGMA block to a Fe_3O_4 core, PEG-modified Polyamidoamine (PAMAM) dendrimer shell with Fe_3O_4 core and mesoporous silica coated on Fe_3O_4, mostly coated with an anticancer drug and used for controlled release of cytostatic drugs into the tumor site by means of pH change [100].

7. Nanogels: They are three-dimensional, water soluble, cross-linked hydrogel materials in the nanoscale size range with a high loading capacity for guest molecules and act as drug carrier systems [101]. Nanogels are the novel drug delivery systems for both hydrophilic and hydrophobic drugs [102]. There are some anti-tumor drugs *viz.*, Cisplatin, DOX, 5-Flurouracil, Heparin, Temozolomide etc. used in cancer therapy by incorporation through nanogels. The pH- and temperature-responsive nanogels made up of maleic acid poly-(N-isopropylacrylamide) polymer loaded with DOX have been frequently employed in the cancer treatment, where DOX is delivered at a specific pH and temperature. Chitin-polymerized DOX nanogels have been also used for treatment of breast cancer [103]. Several nanogel formulations used in cancer therapy are listed elsewhere [104]. The pH-sensitive PEGylated nanogel loaded with anti-tumor drug has proved to be a promising nano-sized carrier for anticancer drug delivery systems against the human breast cancer cell line MCF-7 [105]. Bardajee et al. [101] have prepared a thermo-/pH-Sensitive Nanogels Comprising Salep Modified Graphene Oxide (SMGO) with branched N-Isopropylacrylamide (NIPAM) and Acrylic Acid (AA).

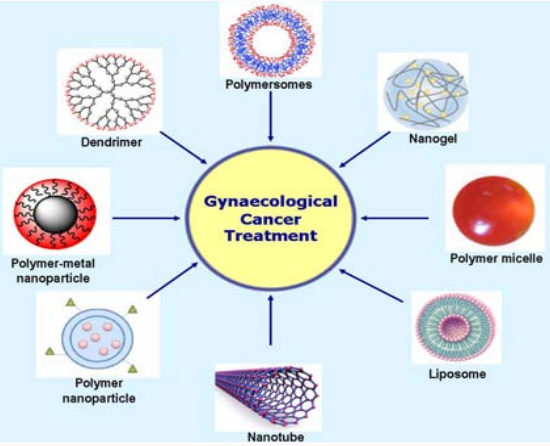

Figure 1: pH-sensitive nanosystems used in anti-cancer drug delivery for treating gynecological cancers.
All these nanosystems have common characteristics of (i) High specificity, (ii) Reduced toxicity, (iii) Controlled drug release, (iv) Enhanced delivery, (v) Dose reduction, and (vi) Diverse routes of administration. All of them are being used/ and have potential to be used successfully in gynecological cancer treatment.

Doxorubicin loaded SMGO/P (NIPAM-co-AA) nanogels showed thermo-/pH-dependent drug release and exhibited enhanced toxicity to HeLa cells when compared to the equivalent dose of the free drug [101]. A synergistic combined chemo-radioisotope therapy of cancer using a pH-dependent hybrid nanogel (hydrogel nanoparticle) platform based on the self-assembly of carboxymethyl cellulose and bovine serum albumin was reported [106]. The pH sensitive polymeric nano-hydrogels attached with an ionizable weak acidic or basic moieties, cationic polymeric Polyethylenimine (PEI), polymeric nano-micelles of pH-responsive natural polymers like albumin and gelatin have also been used as drug delivery systems for treating varied cancers [107]. Peng et al. [108] have synthesised a pH-sensitive nanogels by using a monomer N-[(2,2-dimethyl-1,3-dioxolane)methyl] acrylamide (DMDOMA) bearing an acid cleavable acetal group. These seemed to be a promising and conveniently prepared alternative to existing carrier systems for drug delivery. Thus, nanogels seem to be potential candidate in the development of new nanocarriers for anti-cancer drug delivery. So they can be further investigated for treating gynecological cancers.

Discussion and Conclusion

Despite considerable research in the past decades and plethora of positive results in the preclinical studies, the clinical translation of pH-sensitive nanosystems assisted drug delivery platforms has not progressed incrementally. Some of the facts which appear to be obstacles seem to hinder this progress are: (i) The difference in pH between normal and tumor tissues are not significant enough for generating the pH-responsiveness. Moreover, pH-sensitive nanoparticles remain non-responsive in the perivascular region because the acidic pH need for responsiveness is found in region far from the blood vessels [29]. (ii) In addition to these, selecting a polymer with a critical pH that matches the desired pH range for its application is a major factor in designing an ideal pH-sensitive system. Thus, understanding the chemical structure of the polymer's ionizable moieties, and their respective pKa are indispensable for the design and synthesis of appropriate pH-sensitive DDS [109]. Moreover, attempts have been made to alleviate much concerned cytotoxicity of synthesized NPs by conjugating it with PEG or with any of the zwitterionic polybetaines [110-114]. Further studies are still on to nullify its cytotoxicity, if any. Considering all these, it becomes utmost important to understand the nanotechnological advancement in biomedical applications to date and the challenges that still need to be overcome. That will allow future research to improve on existing pH-sensitive nanoplatforms and to address the current translational and regulatory limitations. Continued translational success will require coordinated communication and collaboration between experts involved in all stages of pharmaceutical development of pH-sensitive drug delivery nanosystems, including pharmaceutical design, manufacturing, cellular interactions and toxicology, as well as preclinical and clinical evaluation.

In all of the aforementioned and other pH-responsive nanosystems reported elsewhere [50,107,115-117], the conventional nano-carriers have been combined with pH-responsive systems that release drug content only under specific acidic pH. Figure 1 summarize all of the pH-sensitive nanosystems reviewed in the present text having potential utilities in treating gynaecological Cancers. However, some of the systems discussed here are yet to be investigated for gynecological cancers. But all of them seem to have tremendous potential for successfully delivering drugs at the targeted gynecological tumor sites/tissues, as the case may be. Therefore, it will not be an exaggeration to state that the pH sensitive nanomedicine could turn to be a unique system for treating gynecological cancers (and other cancers, as well), if developed and delivered with utmost care.

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