Review

Targeted Cancer Therapy via pH-Functionalized Nanoparticles: A Scoping Review of Methods and Outcomes

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Abstract: (1) Background: In recent years, several studies have described various and heterogenous methods to sensitize nanoparticles (NPs) to pH changes; therefore, in this current scoping review, we aimed to map current protocols for pH functionalization of NPs and analyze the outcomes of drug-loaded pH-functionalized NPs (pH-NPs) when delivered in vivo in tumoral tissue. (2) Methods: A systematic search of the PubMed database was performed for all published studies relating to in vivo models of anti-tumor drug delivery via pH-responsive NPs. Data on the type of NPs, the pH sensitization method, the in vivo model, the tumor cell line, the type and name of drug for targeted therapy, the type of in vivo imaging, and the method of delivery and outcomes were extracted in a separate database. (3) Results: One hundred and twenty eligible manuscripts were included. Interestingly, 45.8% of studies (n = 55) used polymers to construct nanoparticles, while others used other types, i.e., mesoporous silica (n = 15), metal (n = 8), lipids (n = 12), etc. The mean acidic pH value used in the current literature is 5.7. When exposed to in vitro acidic environment, without exception, pH-NPs released drugs inversely proportional to the pH value. pH-NPs showed an increase in tumor regression compared to controls, suggesting better targeted drug release. (4) Conclusions: pH-NPs were shown to improve drug delivery and enhance antitumoral effects in various experimental malignant cell lines.

Keywords: pH-responsive nanoparticles; drug delivery; cancer therapy; nanocarriers

1. Introduction

The advancements made in nanotechnology in recent years has led to an unprecedented interest in developing targeted therapies for cancer based on nanoparticles (NPs). NPs are defined as nano-sized particles with diameters ranging from 1 to 100 nm [1–3]. Although small, NPs have a large surface area and can be used as carriers for a wide range of peptides [4], antibodies [5], drugs [6], or contrast agents [7]. NPs are widely used as a platform for delivering drugs due to their stable high carrier capacity and their ability to accumulate in tumors through the enhanced permeation and retention effect (EPR) [8,9]. Because of the accelerated angiogenesis, tumors are supplied by immature blood vessels with a defective architecture with wide endothelial gaps through which molecules smaller than 700 nm can penetrate [10–12]. This characteristic represents the core which led to NPs becoming an important platform for research into cancer theranostics. Inversely, many tumors are heterogenous and possess a dense extracellular matrix which increases interstitial pressure by blocking the passive transport of NPs from the peritumoral vessels [9], which
explains why NPs mostly accumulate in the peritumoral region but fail to penetrate the deep tumoral tissue in experimental applications.

Studies have described techniques to improve the penetration of NPs by using the tumor microenvironment as a targeting site for NPs. One of the constant distinct features of the tumoral microenvironment is the acidic pH, between 0.3 to 0.7 units lower than the pH of normal tissue [13]. Based on this trait, several studies have designed functionalized NPs, making them responsive to pH changes. Once the pH-functionalized NPs (pH-NPs) penetrate through the endothelium via the EPR effect, they respond to the acidic pH and may either disintegrate and release drugs or change their size and shape, thus enhancing their capacity to diffuse towards the tumors’ core. In recent years, several studies have described various and heterogenous methods to sensitize NPs to pH changes; thus, in this current scoping review, we aimed to map current protocols for pH functionalization and analyze the antitumoral outcomes of drug-loaded pH-NPs.

2. Materials and Methods

2.1. Literature Search and Study Selection

As previously described [14–16], a systematic search of the PubMed database was performed for all published studies relating to in vivo models of anti-tumor drug delivery via pH-responsive NPs using the following search algorithm: pH AND nanoparticles AND cancer AND delivery AND in vivo. The systematic search was carried out by adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines which were adapted to experimental studies [17]. The PRISMA checklist was followed to conduct the methodology. Inclusion criteria were used according to the Problem/Population, Intervention, Comparison, and Outcome (PICO) formula (Table 1). All studies published in English from the 1st of January 2017 to the 31th of December 2021 describing drug-loaded pH-responsive NPs for targeted delivery in tumors were selected for full-text review. The experimental lot (population) consisted of pH-functionalized nanoparticles tested in vitro to assess pH responsiveness and in vivo to assess the antitumoral effects of pH-NPs loaded with chemotherapeutics. Embryos, cell cultures, tumor spheroids, and human studies were excluded. Nanogels or nano-emulsions were excluded. The intervention was defined as administration of pH-responsive conjugated NPs in tumor-bearing animals. Comparison criteria were further selected from subgroups of the included studies. Primary outcomes were tumor uptake of pH-NPs and tumor regression rate.

Table 1. Overview of inclusion and exclusion criteria.

| Inclusion Criteria | Exclusion Criteria |
|--------------------|-------------------|
| Experimental studies | Clinical studies |
| Full text available in English | Full text not available/other language used |
| Testing of pH-NPs in vitro and in vivo (animal model) | In vitro/in vivo only |
| Descriptive data on type and synthesis of NPs | Type of NPs not named/method of synthesis not described |
| Descriptive data on pH functionalization method | No detailed data on how the NPs were functionalized |
| Data on animal model and malignant cell line used | No data on animal model/malignant cell line |
| pH-NPs used to deliver chemotherapeutics | Other use of pH-NPs (e.g., tumor imaging, hyperthermia) |
| Analysis of tumor uptake of pH-NPs and tumor regression | No data on tumoral response to pH-NPs |
| Detailed description of methodology (is the method reproducible?) | Methods not reproducible based on given data (requiring supplemental data from authors) |
| ARRIVE score ≥ 15 | ARRIVE score < 15 |

2.2. Data Analysis

The following data information regarding each included study was extracted: the author name, the year of publication, the type of NPs, the pH sensitization method, the in vivo model, the tumor cell line, the type and name of drug used for targeted therapy, the type of in vivo imaging, method of delivery, and the outcomes regarding the cellular uptake of NPs.
2.3. Quality Assessment

Two authors (SM and BCM) independently examined the title and abstract of citations, and the full texts of potentially eligible studies were obtained; disagreements were resolved by discussion. The Essential 10 ARRIVE guidelines were used to quantify the quality of included studies [18]. Each study was marked for each ARRIVE item with 0 if the data were lacking, 1 if the data were incomplete, and 2 if the data were complete; thus, the final score of each article could range from zero to a maximum of twenty. Only studies with a minimum ARRIVE score of 14 were included (Figure 1). The reference lists of retrieved papers were further screened for additional eligible publications.

![ARRIVE scores](image)

**Figure 1.** ARRIVE scores breakdown of included studies.

3. Results

3.1. Overview of Included Studies

An initial search of PubMed database found 2686 articles. After triage of title and abstract, 324 full texts were assessed for inclusion. Records based on the title and abstract were excluded if they did not answer our research question: “Can pH functionalized NPs be used as drug carriers for targeted, in vivo, cancer therapy?”. Further, records were excluded if any of the exclusion criteria were obvious within the title or abstract. Eligible full texts were triaged according to the same principles (Table 1). The PRISMA flowchart shows a breakdown of excluded full texts (Figure 2). One hundred and twenty fully eligible manuscripts were included for in-depth analysis [19–139] (Table S1). Interestingly, 45.8% of studies (n = 55) used polymers to construct nanoparticles—either natural polymers (such as chitosan) or synthetic ones (Tables 2 and 3). The most common pH sensitization method used acid-labile bounds (e.g., hydrazone, ester, imide) (Tables 2–6). BALB/c mice were part of the chosen experimental model in 98.3% (n = 118) of studies. pH-NPs were used in a wide array of malignancies, including breast carcinoma (40%, n = 48), hepatocarcinoma (14.1%, n = 17), lung cancer (11.6%, n = 14), colon carcinoma (6.6%, n = 8), cervical cancer (6.6%, n = 8), and melanoma cell lines (1.6%, n = 2) (Tables 2–6). Fluorescent imaging (70.8%, n = 85) and transmission electron microscopy (24.1%, n = 29) were used to quantify in vivo biodistribution of pH-NPs. Most studies (80.8%, n = 97) used control NPs which were not pH-sensitized to compare biodistribution and tumor penetration. Furthermore, almost all researchers (n = 119) compared cargo release from NPs in both physiological and acidic pH. Four studies proved that NPs increase in size when exposed to low pH, due to associated swelling and widening of membrane gaps, before drug release. The mean acidic pH value used in the current literature is 5.7 [5–6.8], which is significantly lower than that measured in tumor microenvironments, which can vary between 6.7 and 7.1, as previously reported.
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Figure 2. PRISMA flowchart.

Table 2. Summary of methods used in studies.

| Type of NPs          | No. of Studies |
|----------------------|----------------|
| Polymeric            | 55             |
| Lipid                | 12             |
| MSN                  | 13             |
| Metallic             | 11             |
| Other                | 29             |

| pH Sensitization Method                  | No. of Studies |
|-----------------------------------------|----------------|
| pH-labile linkers                       | 70             |
| pH-triggered structural changes         | 35             |
| pH-triggered hydrophobic to hydrophilic transition | 8 |
| Other methods                           | 7              |

| Cancer Model                            | No. of Studies |
|-----------------------------------------|----------------|
| Breast malignant cell lines             | 48             |
| (4T1, MCF-7, MDA-MB-231)                |                |
| Cervical malignant cell lines           | 8              |
| (HeLa)                                  |                |
| Lung malignant cell lines               | 14             |
| (A549)                                  |                |
| Colorectal malignant cell lines         | 8              |
| (CT-26, HCT116, SW480)                  |                |
| Liver malignant cell lines              | 17             |
| (H22, HepG2, SMMC 7721)                 |                |
| Other                                   | 25             |

| Types of Chemotherapeutics              | No. of Studies |
|-----------------------------------------|----------------|
| Doxorubicin                             | 69             |
| Paclitaxel                              | 9              |
| Other                                   | 42             |
Table 3. Overview of polymeric NPs: structure, pH sensitization method, tumor type, and delivered drug.

| First Author | Publication Year | Structure of NPs | pH Sensitization Method | Tumor Type | Drug |
|--------------|------------------|------------------|--------------------------|------------|------|
| Adeyemi [19] | 2019             | FA-chitosan-PEG-polyethyleneimine | pH-triggered structural changes | KYSE 30 squamous cell carcinoma | Endostatin |
| Cao [21]     | 2019             | TAT peptide-polyphosphoester lactobionic acid-chitosan-lipoic acid | pH-sensitive transactivator of transcription (TAT) | MDA-MB-231 breast carcinoma cell line | Doxorubicin |
| Chen [23]    | 2018             | Poly(ethyleneimine) | pH-labile amide linkers | HepG2 liver cancer | Doxorubicin |
| Chen [25]    | 2020             | TPGS-HA polymer-PEG | pH-labile amide linkers | PCl3 prostate cancer | Docetaxel |
| Cheng [30]   | 2019             | Polyoxyethyleneimine-urethanes | pH-labile borate ester linkers | MCF-7 breast carcinoma cell line | Docetaxel |
| Cheng [28]   | 2018             | carboxymethyl chitosan | pH-labile hydrazone linkers | MCF-7 breast carcinoma cell line | Doxorubicin |
| Cui [31]     | 2017             | transferrin-PEG | pH-labile hydrazone linkers | MCF-7 breast carcinoma cell line | Doxorubicin |
| Debele [32]  | 2017             | PEG-methacrylamide-tocopheryl succinate-histidine | pH-labile amide linkers | HCT116 colon carcinoma | Doxorubicin |
| Deng [33]    | 2019             | PEG-methylpropenoic acid-glycerol-cinnamaldehyde | pH-labile cinnamylaldehyde linkers | 4T1 breast carcinoma cell line | Doxorubicin |
| Du [36]      | 2017             | PEG-PTTMA | PTTMA disassembly in acidic pH | HeLa cervical cancer | siRNA |
| Fan [39]     | 2017             | polyethyleneimine-PEG | pH-labile borate ester linkers | 4T1 breast carcinoma cell line | siRNA |
| Fang [40]    | 2020             | chitosan-polysaccharide | pH-labile hydrazone linkers | Panc-1 pancreatic cancer | Curcumin |
| Feng [41]    | 2020             | PEG-PAH-DMA poly (L-γ-glutamylcarboxyscin-RBC membrane | pH-triggered structural changes | A549 NSLC cell line | Paclitaxel |
| Gao [44]     | 2017             | PLGA-polyvinyl alcohol | hydrophobic to hydrophilic transition | MDA-MB-231 breast carcinoma cell line | Paclitaxel |
| Gibbens-Bandala [45] | 2019 | U11 peptide-PLGA | pH-triggered structural changes | A549 NSLC cell line | Paclitaxel |
| Gong [47]    | 2018             | PEG-PMTT | hydrophobic to hydrophilic transition | CT-26 colon carcinoma | Docetaxel |
| Guo [49]     | 2018             | PBLG-Sericin | pH-labile carboxyl linkers | A549 NSLC cell line | Methotrexate |
| Guo [51]     | 2020             | DMA-PEG | pH-triggered structural changes | MCF-7 breast carcinoma cell line | Doxorubicin |
| Hong [53]    | 2019             | PEG-methylpropenoic acid-glycerol-cinnamaldehyde | pH-labile cinnamylaldehyde linkers | 4T1 breast carcinoma cell line | Doxorubicin and Curcumin | Paclitaxel |
| Jin [57]     | 2020             | PBA | pH-triggered structural changes | A549 NSLC cell line | Paclitaxel |
| Jung [58]    | 2020             | PLGA | pH-triggered structural changes | MG glioblastoma | Doxorubicin |
| Khan [61]    | 2020             | lactose myristoyl carboxymethyl chitosan-chitosan-PEG-acetyl histidine | pH-triggered structural changes | Huh-7 hepatocellular carcinoma | Adriamycin |
| Kou [64]     | 2017             | lactose myristoyl carboxymethyl chitosan-chitosan-PEG-acetyl histidine | pH-triggered structural changes | CT-26 Pulmonary Metastasis Model | Piperlongumine |
| Lee [66]     | 2018             | DGL-PEG-Tat-KK-DMA | pH-labile amide linkers | HepG2 liver cancer | Doxorubicin |
| Li [70]      | 2018             | RGD-PEG-Arginine-SA | pH-labile hydrazone linkers | HN6 squamous cell carcinoma | GNA002 |
| Li [73]      | 2020             | PDA-HA | pH-labile PDA coating | 4T1 breast carcinoma cell line | Cisplatin |
| Liu [79]     | 2018             | polyethyleneimine-PEG | pH-labile acetal linkers | BT 474 breast carcinoma | Bortezomib |
| Luo [87]     | 2021             | PEG-TAT-HA | pH-triggered structural changes | H22 hepatocellular carcinoma | Disulfiram |
| Mhatre [89]  | 2021             | polyethyleneimine-PEG | pH-triggered structural changes | MDA-MB-231 breast carcinoma cell line | Doxorubicin |
| Palanikumar [96] | 2020 | ATRAM-BSA-PLGA | pH-labile ester bonds | MCF-7 breast carcinoma cell line | Doxorubicin |
Table 3. Cont.

| First Author    | Publication Year | Structure of NPs                       | pH Sensitization Method                        | Tumor Type                      | Drug     |
|-----------------|------------------|----------------------------------------|------------------------------------------------|----------------------------------|----------|
| Qu [100]        | 2018             | carboxymethyl chitosan                 | pH-labile phenylboronic acid pinacol ester     | HepG2 liver cancer               | Doxorubicin |
| Quadir [101]    | 2017             | PEG-PPLG                               | pH-labile amine linkers                        | MCF-7 breast carcinoma cell line | Doxorubicin |
| Ray [102]       | 2020             | PEG                                    | pH-labile amine linkers                        | PANC-1 pancreatic cancer         | Gemcitabine |
| Saravankumar [103] | 2019           | APT-PLGA-PVP-AS1411 aptamer           | pH-triggered structural changes                 | A549 NSLC cell line              | Doxorubicin |
| Shi [105]       | 2018             | PEG-PLH                                | pH-labile PSD linker                            | A549 NSLC cell line              | siRNA    |
| Shi [106]       | 2021             | PEG-PLL-DMA                            | pH-labile amide linkers                        | A549 NSLC cell line              | siRNA    |
| Soe [107]       | 2019             | poloxamer-Ti-EDC-NHS                  | NR                                              | MDA-MB-231 breast carcinoma cell line | Doxorubicin |
| Su [108]        | 2020             | PEG-PMT                                | pH-labile toether linkers                      | Colon26 cell line               | Docetaxel |
| Wang [113]      | 2017             | RGD-PLGA-PEG                           | pH-labile amine linkers                        | MCF-7 breast carcinoma cell line | Doxorubicin |
| Wang [115]      | 2018             | chitosan-graphene oxide               | pH-triggered structural changes (less electrostatic interaction) | HeP2 liver cancer              | Doxorubicin |
| Wei [118]       | 2020             | PEG                                    | pH-labile amine linkers (schiff base)          | B16F10 melanoma                 | Doxorubicin |
| Xiong [122]     | 2019             | TPGS-PEG                               | pH-labile hydrazone linkers                    | MCF-7 breast carcinoma cell line | Doxorubicin |
| Xu [123]        | 2018             | DTPA-PEG-DMA                           | pH labine amine linkers                        | PC3 prostate cancer              | Doxorubicin |
| Xu [124]        | 2021             | chitosan                               | pH-labile ester linkers                        | HeP2 liver cancer MDA-MB-231 breast carcinoma cell line | Doxorubicin |
| Yadav [125]     | 2020             | RGD-chitosan-Cy5.5                     | pH-labile amine linkers                        | Hep2 liver cancer MDA-MB-231 breast carcinoma cell line | Doxorubicin |
| Yan [126]       | 2017             | POEAd-galactose-LA                     | pH-labile ester linkers hydrophobic to hydrophilic transition (PDPA) | Hep2 liver cancer MCF-7 breast carcinoma cell line | Doxorubicin |
| Yang [127]      | 2018             | glycol Chitosan-PDPA                   | pH-labile ester linkers hydrophobic to hydrophilic transition (PDPA) | MCF-7 breast carcinoma cell line | Doxorubicin |
| Yu [128]        | 2019             | PLGA-CPT-DMMA-PEI                     | pH-triggered structural changes                 | MCF-7 breast carcinoma cell line | Doxorubicin |
| Zhang [129]     | 2017             | TPGS-MSN                               | pH-labile ester linkers                        | hepatocellular carcinoma        | Doxorubicin |
| Zhang [131]     | 2018             | DMA-Cystamine-PEG                      | pH-labile ester linkers                        | A549 NSLC cell line             | Paclitaxel |
| Zhou [138]      | 2020             | polyphosphazene                        | pH-labile hydrazone linkers                    | HeLa cervical cancer            | Doxorubicin |

Legend: FA, folic acid; TPGS, tocopheryl polyethylene glycol 1000 succinate; HA, hyaluronic acid; PEG, polyethylene glycol; PTTMA, poly(2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane methacrylate; DMA, dimethylmaleic acid; PAH, polyallylamine; RBC, red blood cell; PLGA, poly(lactic-co-glycolic acid); PPMT, poly(o-pentadecalactone-co-N-methylidiethyleneamine-3,30-thiodipropionate; PBLG, poly(c-benzyl-L-glutamate); U11 peptide, urokinase plasminogen activator receptor (uPAR) targeting peptide; PEI, polyethyleneimine; PLA, poly(lactic acid); PBA, phenylboronic acid; DGL, dendrigraft poly-L-lysine; TAT, tumor-associated antigens; RGD, arginine-glycine-aspartic peptide; DTPA, 3,3‘-dithiodipropionic acid; Cy5.5, cyanine; SA, stearic acid; PDA, hydrochloride dopamine; ATRAM, acidity-triggered rational membrane peptide; BSA, bovine serum albumin; PPLG, poly (γ-propargyl L-glutamate); APT, aptamer; PVP, poly(N-vinylpyrrolidone); PLH, poly(L-histidine); PLL, poly-L-lysine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; NHS, N-hydroxsuccinimide; PMT, poly(ω-pentadecalactone-co-N-methylidiethyleneaminesebacate-co-2,2’-thiodiethylene sebacate); DTPA, 3,3′-dithiodipropionic acid; POEAd, poly(ortho ester diamide); LA, lactobionic acid; PDPA, poly(2-(diisopropylamino)ethyl methacrylate); CPT, C18-PEG2000-TPP.
Table 4. Overview of mesoporous silica NPs: structure, pH sensitization method, tumor type, and delivered drug.

| First Author | Publication Year | Structure of NPs | pH Sensitization Method | Tumor Type | Drug |
|--------------|------------------|------------------|-------------------------|------------|------|
| Chen [24]    | 2020             | MSN-citraconic-poly-L-lisine | acid-labile disulfide linkers | 4T1 breast carcinoma cell line | Doxorubicin |
| Cheng [27]   | 2017             | Polydopamine-FA-PEG-MSN | pH-labile polydopamine coating | HeLa cervical cancer | Doxorubicin |
| Ding [34]    | 2020             | MSN-carboxymethyl chitin-GRP78 peptide | pH-labile thioketal linkers | H22 hepatocellular carcinoma | Doxorubicin |
| Ding [35]    | 2020             | MSN-lipidbilayer-TLS1a aptamer | pH-labile TAT peptide | 4T1 breast carcinoma cell line | Doxorubicin |
| Kundu [65]   | 2020             | MSN-FA | pH-labile PAA linker | MCF-7 breast carcinoma cell line | Umbelliferone |
| Li [73]      | 2020             | Gal-P123-MSN | pH-triggered structural changes (DC lipid) | Huh-7 hepatocellular carcinoma | Irinotecan |
| Li [68]      | 2017             | DM1-MSN-PDA | pH-labile PDA coating | SW480 colorectal cancer cell line | EpCAM |
| Liao [76]    | 2021             | Chitosan-MSN | pH-labile imidazole linkers | 4T1 breast carcinoma cell line | Doxorubicin |
| Liu [80]     | 2019             | MSN | pH-labile calcium carbonate | LNCaP-AL prostate carcinoma | Doxorubicin |
| Mu [94]      | 2017             | MSN-PLH-PEG | hydrophobic to hydrophilic transition | H22 hepatocellular carcinoma | Sorafenib |
| Saroj [104]  | 2018             | MSN | pH-labile PAA linker | PC3 prostate cancer | Bicalutamide |
| Zhang [130]  | 2017             | MSN-pH-responsive peptide | pH-responsive peptide | MCF-7 breast carcinoma cell line | Doxorubicin |
| Zhao [136]   | 2018             | MSN-TPGS | pH-labile ester linkers | MCF-7 breast carcinoma cell line | Doxorubicin |

Legend: MSN, mesoporous silica nanoparticles; FA, folic acid; PEG, polyethylene glycol; GRP78P, glucose regulated protein 78 peptide; TAT, tumor-associated antigens; Gal, gala tosyl; DM1, maytansinoid conjugate; PDA, hydrochloride dopamine; PLH, D-alpha-tocopherol polyethylene glycol 1000-succinate; PAA, polyacrylic acid.

Table 5. Overview of gold NPs: structure, pH sensitization method, tumor type, and delivered drug.

| First Author | Publication Year | Structure of NPs | pH Sensitization Method | Tumor Type | Drug |
|--------------|------------------|------------------|-------------------------|------------|------|
| Aguilar [20] | 2021             | polycaffeic acid-FA-Au | pH-labile catecholeboronic acid linkers | SCC7 squamous cell carcinoma | Bortezomib |
| Essawy [38]  | 2020             | Au-hydrazine | pH-labile hydrazone linkers | HBPC oral carcinoma | Doxorubicin |
| Guo [50]     | 2018             | Au-Chitosan-AS1411 aptamer | pH-triggered structural changes | A549 lung cancer cell line | Methorexate |
| Kumar [63]   | 2020             | Au | pH-labile peptide linker (Lys-Phe-Gly) | BT 474 breast carcinoma | Doxorubicin |
| Liu [81]     | 2018             | Au-iron oxide-PEG | pH-labile oleic acid linkers | SGC-7901 gastric adenocarcinoma | Herceptin |
| Mahalunkar [91]| 2019            | Au-PVP-FA | pH-triggered structural changes | MCF-7 breast adenocarcinoma | Curcumin |
| Sun [110]    | 2019             | Au-AS1411 aptamer | pH-triggered structural changes | HeLa cervical cancer | Doxorubicin |

Legend: FA, folic acid; Au, gold; PEG, polyethylene glycol; PVP, polyvinylpyrrolidone.
Table 6. Overview of lipid-based NPs: structure, pH sensitization method, tumor type, and delivered drug.

| First Author | Publication Year | Structure of NPs | pH Sensitization Method | Tumor Type | Drug |
|--------------|------------------|------------------|-------------------------|------------|------|
| Juang [59]   | 2019             | lipid-PEG        | pH-labile imide linkers | HCT116 colon carcinoma | Irinotecan and microRNA |
| Li [69]      | 2017             | TF-PEG-GMS       | pH-labile hydrazone linkers | A549/DTX lung cancer cell line | Docetaxel and Baicalin |
| Li [71]      | 2019             | LDL-OA           | pH-labile hydrazone linkers | 4T1 breast carcinoma cell line | Doxorubicin |
| Sun [111]    | 2021             | DSPE-PEG         | pH-triggered structural changes | LNCaP-AI prostate carcinoma | Doxorubicin |
| Tan [112]    | 2017             | PAA-OA           | pH-labile oleic acid linkers | A549 NSCL cell line | Erolitinib |
| Men [92]     | 2020             | lipid-HA-PBAE    | pH-triggered structural changes | A549 NSCL cell line | Doxorubicin |
| Cavalcante [22] | 2021       | DSPE-PEG-OA      | pH-labile oleic acid linkers | 4T1 breast carcinoma cell line | Doxorubicin |
| Li [67]      | 2017             | DSPE-PEG         | pH-labile imine linkers | SAS squamous carcinoma cell line | Daunorubicin and Irinotecan |
| Lo [85]      | 2020             | DSPE-PEG         | pH-labile oleic acid linkers | HepG2 liver cancer | Hydroxycamptothecin |
| Ma [90]      | 2021             | DSPE-PEG         | pH-triggered structural changes | A549 NSCL cell line | Erolitinib |
| Pang [98]    | 2020             | lipid-polymeric NPs | pH-labile dihydrazide linkers | MCF-7 breast carcinoma cell line | Methotrexate |

Legend: PEG, polyethylene glycol; TF, transferrin; GMS, glyceryl monostearate; PAA, polyacrylic acid; HA, hyaluronic acid; PBAE, poly(b-amino ester; DSPE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; OA, oleic acid.

3.2. Types of NPs Used

The sensitization of various NPs to acidic pH was measured. Those that were polymeric in nature were most common (Tables 2 and 3); however, mesoporous silica nanoparticles (MSNPs) (Table 4), gold-based NPs (Table 5), or lipid-based NPs (Table 6) were other common options. Polymeric NPs were synthesized through emulsion–solvent evaporation methods or by nanoprecipitation. Polymers have the advantage of being biocompatible and biodegradable and can be designed to either incorporate drugs or simply attach drugs to their matrix via pH-labile linkers. Chitosan was commonly used to form nanocomposites because it is a positively charged biocompatible polymer with good stability in blood circulation which can form complexes with anionic peptides. Another way of using polymers in the design of pH-NPs is by coating the surface of other types of NPs to increase in vivo stability (e.g., PEGylated lipid NPs) (Table 6). Polyethylene glycol (PEG) is hydrophilic and biocompatible, thus coating the surface with PEG (e.g., PEGylation) ensured a longer and more stable intravascular circulation with low immunogenicity. MSN-NPs were another widely used platform for designing pH-responsive drug carriers (11.6%, n = 14) synthesized via the solution–gel method (Table 4). Their main advantage is their porous structure which allows inner encapsulation of drugs, but also the surface linkage of tumor-targeting peptides (e.g., folic acid, transferrin) and pH-responsive binders (e.g., imidazole, hydrazine) can prove useful too.

3.3. Outcomes of pH-NPs

When exposed to in vitro acidic environment, without exception, pH-NPs released drugs inversely proportional to the pH value (Figure 3). In all scenarios, both control and pH-NPs showed similar biodistribution and good stability in vivo; however, pH-NPs showed an increase in tumor regression compared to controls, suggestive of better targeted drug release. As seen in Figure 4, the volume of tumors was lower in groups treated with pH-NPs compared to non-pH-NPs.
Polymers were the most common nanomaterials used in the synthesis of pH-NPs. Our results show that NPs may be used as pH-responsive platforms with excellent results in tumor penetration and tumor regression rates. pH-NPs, regardless of being metallic or polymeric, were shown to have good tumor penetration in most experimental results in tumor penetration and tumor regression rates. pH-NPs. Light gray shows rate (%) of drug released in acidic pH (lowest value used in each study).

Figure 3. Rate of cumulative drug release for each of the included studies. Dark gray area shows rate (%) of drug released at a physiological pH (7.4). Light gray shows rate (%) of drug released in acidic pH (lowest value used in each study).

Figure 4. Volume of tumor (mm\(^3\)) at the end of experiment for each of the included studies. Dark gray area shows the tumor volume for specimens treated with non-pH-NPs. Light gray area shows the tumor volume for specimens treated with pH-NPs.

4. Discussion

Our results show that NPs may be used as pH-responsive platforms with excellent results in tumor penetration and tumor regression rates. pH-NPs, regardless of being metallic or polymeric, were shown to have good tumor penetration in most experimental malignant cell lines in vivo.

Polymers were the most common nanomaterials used in the synthesis of pH-NPs. Besides being used for surface coating to increase the colloidal stability of NPs, polymers (e.g., PEG, PLGA, PHA) were used in the core structure of NPs, making polymeric NPs...
a widely used platform due to their key advantages: biocompatibility, high stability, non-toxicity, easy synthesis, and versatility. Chemotherapeutics can be linked onto or within the polymers via electrostatic interactions. Once assembled, polymeric NPs have high stability in blood circulation and can maintain the EPR effect, which allows them to escape in the tumoral microenvironment, where drugs are released in a controlled fashion [140]. Mesoporous silica nanoparticles (MSN NPs) were also commonly used to design pH-responsive nanocarriers. The main advantage of MSN NPs is their large surface area and large porous structure, in which a high volume of drugs can be encapsulated. Their surface can be also chemically modified to attach various linkers which react to pH changes [141]. Lipid NPs are usually spherical in shape and formed by a bilayer lipid membrane and an aqueous core. They are highly biocompatible and can transport hydrophilic, hydrophobic, and lipophilic drugs; however, lipid NPs can be cleared by the reticuloendothelial system. For this reason, their surface is usually coated with polymers (e.g., PEGylation) to increase their biostability [142]. Gold NPs can be pH-functionalized using surface pH-responsive linkers. Gold NPs have unique optical characteristics, making them suitable for cancer theranostics and photothermal therapy [143].

The tumor specificity of pH-NPs was further enhanced using tumor-targeting peptides linked to the surface of NPs which can target specific receptors commonly expressed by cancers. The folic receptor is known to be overexpressed in various tumors [144] and was used as a target for NPs coated with folic acid, which facilitates the receptor-mediated endocytosis of NPs, where drug cargo can be released in the acidic intracellular environment. Other studies used Fe ions attached to the surface of NPs, as many tumors use Fe for cellular proliferation [145]. Increased expression of transferrin on tumors promotes NPs attachment and internalization [146]. Xie et al. [120] used methotrexate as an antitumor agent and also as a tumor-targeting agent due to its structural similarity to folic acid and capacity to bind to folate expressed by tumors. Gong et al. [49] used arginine–glycine–aspartate triad (RGD peptide) which is a low-toxicity, highly stable peptide with increased affinity to integrins, which in turn are overexpressed by tumoral neo-vessels.

Doxorubicin is the most used chemotherapeutic in current experiments. Doxorubicin is an anthracycline with potent antimitotic and cytotoxic activity. Its mechanism of action involves intercalation between base pairs where it inhibits DNA synthesis and, in addition, inhibits topoisomerase II activity, thus reducing DNA replication [147,148]. Despite having excellent antitumor activity, its use is limited by important side effects, such as cardiotoxicity and myelosuppression [148]. In a conjugated form, incorporated in the hydrophobic core of nanocarriers, doxorubicin can be administered in higher doses, and can be released at the tumor site where nanoparticles accumulate through enhanced permeability release or by active tumor targeting through pH-dependent conversion, as demonstrated in the included studies.

Drugs are usually loaded into NPs either through core encapsulation or surface binding. Core encapsulation refers to the organization of NPs around drugs, usually due to their amphipathic property, and the hydrophobic end safeguards the drugs in the center, while the hydrophilic end forms a protective shell, enabling a safe transport of cargo to the tumor. Another way is to attach drugs to the surface of NPs, especially when PEGylation is used to coat the surface. PEG is a stable carrier and binder, and various linkers can be used to attach drugs or tumor-targeting receptors to its surface.

Acid-labile Schiff base linkages were the core from which nanoparticles, regardless of type, were designed to respond to pH changes. Imine Schiff bases undergo hydrolyzation under acidic conditions and such are used as linkers when nanoparticles are assembled. Once the peritumoral acidic pH is sensed, the linkers break, causing disruption of the nanocarriers and release of drugs. In other scenarios, the nanocarriers were coated with tumor-targeting peptides (e.g., folic acid, AS1411 aptamer) which interacted with cancer cells and allowed for the nanocarriers to reach the intracellular environment, via endocytic pathways, where the drugs were released. Another pH sensitization method is the use of electrostatic interactions. pH-NPs were coated with a negative-charged surface which
reverted to a positive charge in the acidic environment, leading to the release of positively charged peptides, which were linked to drugs [42].

Functionalized NPs may become a cornerstone in cancer treatment as they can overcome the barrier of systemic toxicity produced by non-targeted chemotherapeutics and can increase the amount of drug delivered to the tumor. Designing NPs responsive to acidic pH has proven to be a solid option. However, we must consider that, in most studies, the maximal effects of pH-NPs were at a pH lower than 6.5. To ensure similar outcomes in clinical studies, pH-NPs need to be ultra-sensitized to release similar amounts of drugs at pH values of 6.8–7.2, which is the usual pH value in the tumor microenvironment.

5. Conclusions

This scoping review mapped the current methods and outcomes of using pH-responsive nanoparticles to improve drug delivery and enhance antitumoral effects. Regardless of their type and structure, pH-responsive nanoparticles can increase tumor regression rates compared to the controls. Drug delivery, therefore, is dependent on the exposure of NPs to acidic pH.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/gels8040232/s1, Table S1: Detailed Overview of Included Studies.

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